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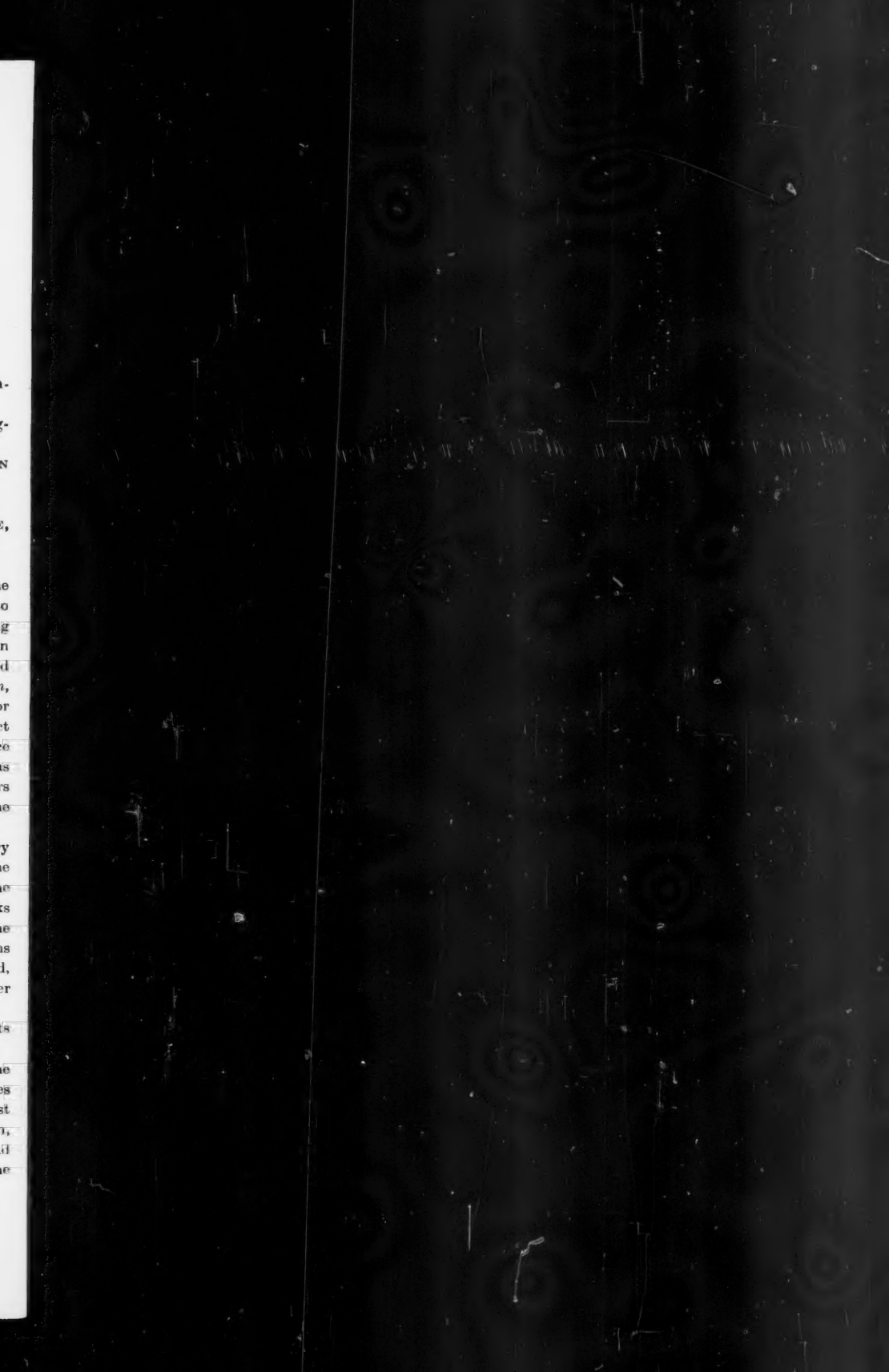

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From Queen Louise's Children's Hospital, Copenhagen.
Chief: Professor OLUF ANDERSEN, M. D.

Intracutaneous and Percutaneous BCG-Vaccination

by PREBEN EILERSEN

In the course of time various methods for performing the BCG-vaccination have been applied. In most places the oral and the subcutaneous applications have been given up, and we are left with the intracutaneous and the percutaneous methods of vaccination, which for the time being are the methods preferred.

In Denmark the intracutaneous technique is the one most commonly applied. It is known that this form of vaccination is often followed by secretion and crustation at the site of vaccination, in some cases by long-standing suppuration and in a few cases by local abscess formation. Furthermore, now and then glandular swelling and axillary glandular abscess are to be seen. The post-vaccination scars are in isolated cases disfiguring and visible for years. Certainly these inconvenient local reactions are lowered to a minimum by an experienced worker, but still they contribute considerably to the dislike for BCG-vaccination which is now and then encountered.

For some years experiments have therefore been carried out at the Queen Louise's Children's Hospital with percutaneous vaccination—in the hope of obtaining a vaccination which can be performed without these disadvantages by anybody.

Percutaneous BCG-vaccination was applied first in 1939 by ROSENTHAL, who produced 30–40 punctures through the skin by a needle and then rubbed a drop of vaccine into the punctures. Apart from local redness and infiltration no complications were observed. Three months after the vaccination 99 % were positive. Out of a control group vaccinated intracutaneously 98.4 % were positive 3 months after the vaccination.

In 1939 a technique was indicated by NÈGRE and BRETEY by applying percutaneous scarifications. The scarifications were made by a common vaccination-lancet after which the vaccine was rubbed into the scarifications which were covered by cellophane paper. Out of 100 guinea pigs all were positive in 35 days.

Later percutaneous vaccinations were either performed by ROSENTHAL's or NÈGRE's technique or modifications of these.

BIRKHAUG thus applies an automatic spring lancet supplied with 40 needles which at one time scarifies the skin by means of a spring. BIRKHAUG by 5,000 vaccinations got 98 % positive in 2 months. Rarely small pustules were observed at the site of vaccination. In the following years several reports on good results by applying the percutaneous vaccination were published—DELACHAUX, IMBERT, MATHIESEN, PERDICOLOGOS, WEILL-HALLE, WIDLUND. It is specially pointed out that allergy appears earlier—or in any case just as early—as by the intracutaneous vaccination. As a rule there is only a little redness and infiltration around the scarifications. There were in no cases more severe suppurations or abscesses. The scars are in any case insignificant. WALLGREN's experience is less favourable. He finds just as many local complications by percutaneous as by intracutaneous vaccination and in addition a slower evolution of allergy.

Systematic comparisons of the results of BCG-vaccination carried out by intracutaneous injection and percutaneous scarifications on guinea pigs are described by MØLLER and by BIRKHAUG (3). These experiments showed that the allergy appeared equally quickly with both forms of vaccination and that local complications were less frequent by the percutaneous method. SINDBJERG-HANSEN and MØLLER described 1945 the result of 21 scarification vaccinations in newborn infants carried out at the Queen Louise's Children's Hospital. There were no complications. Eighty-six per cent were Moro-positive after 5 weeks, and out of 13 examined one year after the vaccination 12 were still positive. Since January 1949 BCG-vaccinations have been carried out at the Queen Louise's Children's Hospital—partly intracutaneously and partly percutaneously in order to compare the results of these two methods of vaccination in children.

During the years 1949–51 357 BCG-vaccinations were carried out at the hospital. Children born on even dates have been vaccinated by intracutaneous injection, and children born on odd dates have been vaccinated by percutaneous scarification.

The vaccine has been supplied by the State Serum Institute. The vaccinations were performed by the physicians of the hospital.

The intracutaneous vaccination has been carried out as generally applied in this country. One-tenth ml vaccine containing 3 mg culture per ml has been injected over the deltoid region after cleaning with alcohol. Children below six months of age have been vaccinated in both shoulders, children above six months in one only.

The percutaneous scarification vaccination has been carried out essentially as indicated by NÈGRE and BRETEY. In both shoulder regions 5 one-cm-long scarifications at a space of 1–1 $^1/_2$ mm are made by a vaccination lancet. No bleeding must appear, and at the most single blood-dots. One drop of

vaccine containing 20 mg culture per ml is applied on the scarified skin. Then the vaccine is rubbed down by a glass stick into the skin which is finally covered by a small piece of gauze and a sticking-plaster.

Out of 357 vaccinated individuals 167 were vaccinated by scarification and 190 by intradermal injection. The distribution of age will be seen in Table 1.

TABLE 1

Age distribution.

	0–2 years	2–6 years	> 6 years	
Scarification	60	60	47	167
Intradermal injection	69	79	42	190
	129	139	89	357

The development of allergy was followed in 134 of the vaccinated children by Moro patch test systematically performed every week. After 9 weeks 131 were positive, 2 scarification-vaccinated and 1 intradermally vaccinated did not turn positive and had to be revaccinated. By a positive Moro patch reaction is meant that 10–12 follicles, in a red infiltrated part of the skin, have appeared 72 hours after application of the tuberculin ointment. Furthermore, the Mantoux reaction has been followed systematically in 68 children from week to week. Ten TU have been applied in each test. The reaction is considered positive when the infiltration was greater than or equal to 10 mm.

TABLE 2

Times at which Moro and Mantaux turned positive and weekly number expressed in percentages

	Scarification								Intradermal injection							
Weeks	2	3	4	5	6	7	8	9	2	3	4	5	6	7	8	9
MORO																
Number	3	12	14	11	3	3	4		16	19	20	13	5	4	6	1
%	6	24	28	22	6	6	8		19.0	22.6	23.8	15.5	6.0	4.7	7.2	1.2
MANTOUX																
Number		5	11	3	3	2	1	1	7	11	8	9	1	4	1	1
%		19.3	42.7	11.5	11.5	7.7	3.8	3.8	16.7	26.2	19.0	21.4	2.4	9.5	2.4	2.4

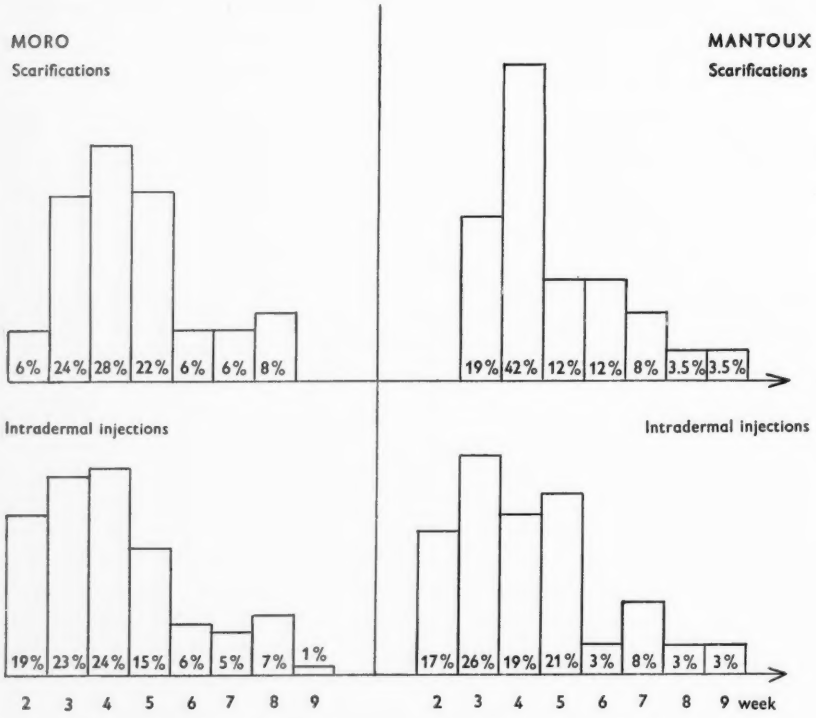
MORO
Scarifications
6% 24% 28% 22% 6% 6% 8%
MANTOUX
Scarifications
19% 42% 12% 12% 8% 3.5% 3.5%
Intradermal injections
19% 23% 24% 15% 6% 5% 7% 1%
2 3 4 5 6 7 8 9
Intradermal injections
17% 26% 19% 21% 3% 8% 3% 3%
2 3 4 5 6 7 8 9 week

Fig. 1. Showing a graphic representation of the time of occurrence of positivity.

The occurrence of positivity is shown in Table 2. A graphic representation of the terms is to be seen in Figure 2. At the abscissa is marked the time for the appearence of allergy, and at the ordinate the percentage turned positive. It should be noted that there is no certain difference for the time of appearance of allergy between scarification and intradermal vaccination.

A follow-up examination of the indivuduals vaccinated has been carried out from February to April 1952. The individuals vaccinated have been asked to report to the outpatients' department at the hospital for examination. However, 24 patients living rather far away were not asked to report. Two patients had died. Out of 333 called-in, 165 = 49.5 % came.

At examination the children were accompanied usually by their mothers, who were asked about the course of the vaccination, especially if any complications had been noticed. As to the children hospitalized a long time after the vaccination, the course had been described in the records.

In addition, the appearance of the vaccination-scar was observed and the

scar was measured. The children got a Moro and a Mantoux-reaction with 10 TU. The tuberculin tests were read after 72–74 h. As a measure for the strength of the Mantoux-reaction the diameter of the infiltration was measured.

TABLE 3

Course and number of complications.

	No complications, redness or infiltrations	Crust	Secretion	Strong secretion	Abscess	Glandular swelling	Glandular abscess
Scarification	70 = 90.9 %		7 = 9.1 %	0	0	0	0
Intradermal injection	7 = 8.0 %	33 = 37.5 %	26 = 29.5 %	16 = 18.2 %	6 = 6.8 %	3 = 3.4 %	1 = 1.1 %

The courses of the vaccinations and the number of complications are shown in Table 3. The first group covers those vaccinations which passed completely normally, that is, without secretion but only followed by redness and infiltration. In the next group are included vaccinations causing secretion which was rapidly followed by crustation. By light secretion is meant non-inconvenient secretion of a few weeks' duration; while by strong secretion is meant prolonged inconvenient secretion, often lasting for months, and finally the groups with local abscess, considerable axillary glandular swelling and going on to glandular abscess in the axilla.

As shown 70 = 90.9 % out of 77 scarifications passed without essential inconvenient reactions, while 7 = 9.1 % were followed by more or less light secretions. Out of 88 punctures only 40 = 45 % passed without inconvenience, that is followed by redness, infiltration or crust. Forty-two = 47.7 % were followed by secretion and 6 by local abscess. In 3 cases there was considerable glandular swelling, and in one of these a glandular abscess which had to be punctured.

The time of observation was between 4 months and 3 years. Nine revaccinated were among those post-examined, viz. 3 puncture vaccinated = 3.4 %, and 6 scarification vaccinated = 7.8 %.

As a measure for allergy Moro patch test and Mantoux test are performed as described. Out of 71 scarification vaccinated—non-revaccinated—70 were Moro-positive, and out of 85 intradermally vaccinated—non-revaccinated—83 were Moro-positive.

In the Mantoux reaction, performed as described, the strength of allergy ought to be more exactly expressed than in the Moro reaction. However, some doubtfulness results from the tuberculin reaction often being weak in babies (JENSEN), and the Moro reaction in these being more sensitive than Mantoux (ANDERSEN). The results appear from Figure 2 which shows no

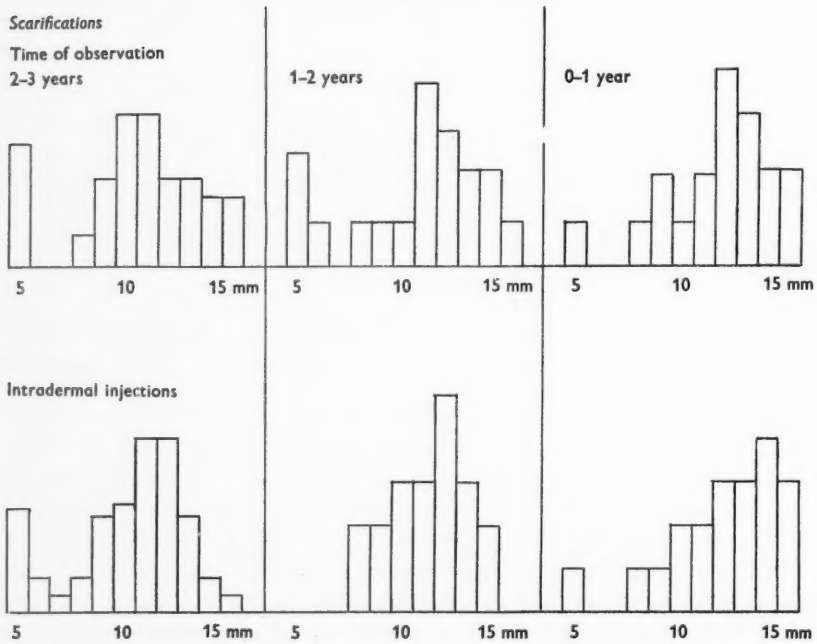

Fig. 2. Showing the distribution in percentages of the strength of the Mantoux-reaction. Abscissae the induration in mm. Ordinate the number in percentages of each group.

certain difference in the persistence of allergy between scarification vaccination and intradermal vaccination.

TABLE 4

Nature and size of the cicatrice.

Scarifications	No scar	Just visible scar		0–½ mm scar	½–1 mm scar
77	50 = 64.9 %	17 = 22.1 %		9 = 11.7 %	1 = 1.3 %
Intradermal injections	No scar	0–2 mm scars	2–4 mm scars	4–6 mm scars	6 mm scars
88	9 = 10.2 %	33 = 37.5 %	24 = 27.3 %	13 = 14.8 %	9 = 10.2 %

Finally the condition of the cicatrices has been examined, Table 4. In 50 scarification vaccinations there were no visible scars. In 17 the scars were just visible as fine linear stripes and in 9 the scars were visible, but were below $^1/_2$ mm broad. In one case only, the scar was strongly visible with a breadth of $^1/_2$–1 mm. No scars showed thickening.

In the intradermally vaccinated group 9 were without scars, 57 had visible but slightly disfiguring scars of 0–4 mm diameter, 21 had scars above 4 mm, and of the latter 12 had thickened obvious scars.

From the examination results it appears that allergy following vaccination develops fairly quickly by intracutaneous and percutaneous BCG-vaccination. In almost every case the percutaneous vaccination passed without inconvenient local reactions for the patient, while the intracutaneous vaccination was followed, in a considerable number of cases, by a long-lasting and troublesome secretion and, in isolated cases, by glandular swelling and glandular abscess.

Concerning the persistence of allergy no certain differences have been demonstrated between the two methods of vaccination.

The scars after the scarification vaccination were most often invisible and in a single case prominent. The scars after the intradermal injections were in almost all cases visible and in some cases prominent and thickened.

This seems to show that the percutaneous scarification method is a method of vaccination which, performed by different doctors, results in the quick development and persistence of allergy, at the same time giving a minimum of complications and none or only insignificant scars from the vaccination. These results seem to encourage further experiments on a far larger material.

Summary

Of 357 vaccinated children 167 were vaccinated by percutaneous scarifications and 190 by intracutaneous injection. One hundred and thirty-four have been followed systematically from week to week by Moro patch test and 68 by Mantoux test. The individuals intracutaneously and percutaneously vaccinated turned positive at approximately the same time. The local changes at the site of vaccination have been followed. No major changes were observed in individual scarification vaccination except for redness, infiltration and perhaps a little secretion. Intradermal vaccination was very often followed by suppuration and in separated cases abscesses. One hundred and sixty-five were post-examined by Moro and Mantoux. No certain difference in the allergy obtained was demonstrated. The scars have been inspected. In individual cases with scarification vaccination none or only insignificant scars were found. In individuals subjected to intradermal vaccination visible scars were often found, in more cases even thickened, disfiguring scars.

Vaccination par le BCG par voie intra-cutanée et percutanée.

Sur 357 enfants vaccinés, 167 le furent par scarifications percutanées et 190 par voie intra-cutanée. 134 ont été suivis systématiquement semaines après semaines par le test de Moro (patch) et 68 par celui de Mantoux. Les sujets vaccinés suivant les deux méthodes eurent leurs réactions positives à peu près au même moment. Les réactions locales furent suivies. Les scarifications n'entraînèrent pas de modifications importantes en dehors d'une rougeur locale, une infiltration et peut-être une légère

sécrétion. Au contraire la vaccination intra-cutanée fut suivie très souvent de suppuration et dans des cas isolés d'un abcès. 165 furent soumis aux tests de Moro et Mantoux sans que l'on ne note de différences de la réaction allergique entre l'un et l'autre. En ce qui concerne les cicatrices, celles-ci furent nulles ou insignifiantes chez les sujets soumis aux scarifications s'opposant aux cicatrices visibles fréquemment trouvées après injection intra-dermique, avec dans beaucoup cas des épaississements et même des cicatrices disgracieuses.

Intracutane und percutane BCG-Impfung.

Von 357 geimpften Kindern wurden 167 durch percutane Scarifizierung und 190 durch intracutane Injektion geimpft. 134 wurden systematisch von Woche zu Woche durch den Moro-Pflastertest und 68 mittels Mantouxtest verfolgt. Die intracutan und percutan geimpften Personen wurden etwa zur gleichen Zeit positiv. Die lokalen Veränderungen an der Impfstelle wurden beobachtet. Bei der Scarifizierung wurden außer Rötung, Infiltration und etwas Sekretion keine größeren Veränderungen registriert. Die Injektionsimpfung wurde oft von Eiterungen und in einzelnen Fällen von Abszeßbildung gefolgt. 165 wurden nach Moro und Mantoux nachuntersucht. Sichere Unterschiede der allergischen Reaktionen konnten nicht demonstriert werden. Die Narben wurden untersucht. Bei den Scarifizierungsfällen wurden keine oder nur unbedeutende Narben untersucht. Bei den durch intracutane Injektion geimpften Individuen wurden oft sichtbare, in mehreren Fällen auch verdickte und entstellende Narben gesehen.

Vacunación intracutánea y percutánea en el B.C.G.

De 357 niños 167 fueron vacunados por escarificaciones percutáneas y 190 por inyección intracutanea. 134 fueron seguidos sistemáticamente semana a semana por el test de Moro y 68 por el test de Mantoux. Los individuos vacunados percutánea y intracutánea se volvieron positivos más o menos al mismo tiempo. Los cambios locales en el lugar de la vacunación fueron seguidos. No se observaron grandes cambios en los individuos vacunados por escarificación excepto color rojo, infiltración y talvez una pequeña secreción. La vacunación por inyección intradérmica fué amenudo seguida por supuración y en casos aislados abcesos. 165 fueron después examinados por Moro y Mantoux. No se observaron claras diferencias en la alergía. Las éscaras fueron estudiadas. En individuos con vacunación por escarificacion se encontraron éscaras insignificantes o ausentes. En individuos sujetos a vacunación por inyección intradérmica se vieron frecuentemente éscaras visibles, en la mayor parte de los casos gruesas.

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From the Foundlings Asylum, Athens.
(Chief: P. J. Lambrinakos.)

Remarks on an Epidemic of Poliomyelitis

by P. J. LAMBRINAKOS, D. S. MELISSAKIS and
DRIVAS HELEN PAPACOSTA

In February 1951 an epidemic of poliomyelitis broke out at the Foundlings Hospital of Athens. The epidemic lasted three months, from February to April 1951 inclusive, and attacked 26 infants 7–27 months old. In 7 different wards only, out of the 20 at the disposal of the Foundation, were there infants affected, i.e. one baby from each one of five wards and 21 infants from the two remaining.

According to their clinical manifestations and the general evolution of the poliomyelitis the 26 cases are classified into three categories.

The first category includes 14 cases of poliomyelitis of paralytic form, following the well-known preparalytic stage in which, with a temperature oscillating between 37.5° and 39° for four to five days, and rhinopharyngeal phenomena—rhinopharyngitis, tonsillitis—8 cases showed neurovegetative symptoms, i.e. sweating and constipation. The examination of the cerebrospinal fluid revealed the common characteristic laboratory findings of the disease. Ten out of fourteen cases in this group survived, and four succumbed, two following Landry's syndrome and two others after an attack of bronchopneumonia.

The second category includes 7 cases in which the poliomyelitis manifested no paralytic phenomena, and the clinical manifestations of the poliomyelitic infection began with phenomena of rhinopharyngitis, tonsillitis and a temperature oscillating between 37.8° and 38° and with neurovegetative symptoms, namely, profuse sweating, constipation and hypersensitivity of the skin.

The lumbar punctures, four in every case, done at three-day intervals revealed in the first three a clear fluid under high pressure as well as protein increase ranging from 0.25 to 0.60 per thousand and cellular elements from 20 to 100 per cmm, at first with a polynuclear predominance and then a lymphocytic one. The last lumbar puncture revealed an entirely normal fluid. The sugar and the chlorides were in all examinations normal. In the above seven cases the poliomyelitic infection lasted 4 to 7 days at the end of which

all the clinical manifestations vanished and the cerebrospinal laboratory findings became normal without consequent paralytic phenomena.

The cases of the second category belong to the non-paralytic forms of poliomyelitis and notably to the poliomyelitic infections which simulate the clinical picture of influenza, gastro-enteritis, tonsillitis or rhinopharyngitis as it occurred in our cases. If we are to admit the new clinical division of the non-paralytic forms of poliomyelitis, a division suggested by MOLLARET, we must classify the cases of the second category in the "apparent forms" of poliomyelitis. Their diagnosis offers great difficulty and is based, first, on the cerebrospinal fluid examination, and secondly on the presence of an epidemic of poliomyelitis and the eventual cohabitation of such patients with others affected by poliomyelitis of paralytic form. These forms were mentioned by us first in Greek medical bibliography, but a number are reported in the world literature.

The third category, constituting the most interesting scientific part of this paper, includes five cases showing clinically neither fever, paralysis nor any other pathologic evidence that could give rise to a suspicion of poliomyelitis. The affected individuals could never be considered as patients; but the lumbar punctures on these cases revealed in the cerebrospinal fluid the well-known laboratory findings of poliomyelitis, i.e. clear fluid under high pressure as well as an increase in protein and cellular elements. Thus, the protein ranged from 0.20 to 0.50 ‰ and the cellular elements from 8 to 80 per cmm and chlorides were at normal levels (see Table).

From the above laboratory findings on cerebrospinal fluid examination it is well established that the third category of cases had to do with a latent form of poliomyelitic infection of the nervous system evidenced only by laboratory findings.

The above latent form of poliomyelitic infection of the nervous system has presumably developed either by localization of the poliomyelitis virus in the anterior horns of the gray matter of the spinal cord, as it occurs in the well known classic form of Heine-Medin disease, or as a slight meningeal form of poliomyelitis.[1] In order to determine the cases belonging to the third category, we proceeded to do lumbar punctures on 22 healthy infants nursed in the two wards where principally most of the cases of the first and second categories of poliomyelitis developed, expecting to detect some latent infection of the nervous system. In all second and third category cases, direct

[1] The above explanation is necessary owing to the fact that many authors actually accept that the cerebrospinal fluid laboratory findings revealed in paralytic or non-paralytic forms of poliomyelitis without clinical meningeal manifestations are not due to an inflammatory change of the meninges but to a meningeal reaction arising from the toxic products of the motor cells of the spinal cord, altered by the inflammation.

TABLE

Showing the different changes of the cerebrospinal fluid in infants attacked by latent poliomyelitic infection of the nervous system.
(Cases of third category.)

Age of infants	Date of lumbar punctures	Laboratory findings in the cerebrospinal fluid							
		Protein per thousand	Cells by cmm	Lymphocytes per cent	Polynuclears per cent	Sugar per thousand	NaCl per thousand	Aspect	Pressure
7 months	10.4. 51	0.40	65	34	66	normal	normal	clear	very increased
	13.4. 51	0.40	55	85	15				
	18.4. 51	0.35	40	80	20				
	23.4. 51	0.25	15	85	15				normal
8 months	10.4. 51	0.45	70	48	52	normal	normal	clear	very increased
	13.4. 51	0.40	60	70	30				
	18.4. 51	0.30	30	80	20				
	23.4. 51	0.20	12	88	12				normal
9 months	10.4. 51	0.50	68	67	33	normal	normal	clear	very increased
	13.4. 51	0.45	50	72	28				
	18.4. 51	0.35	25	80	20				
	23.4. 51	0.20	8	86	14				normal
10 months	10.4. 51	0.45	80	46	54	normal	normal	clear	very increased
	13.4. 51	0.40	70	60	40				
	18.4. 51	0.35	45	75	25				
	23.4. 51	0.25	15	87	13				normal
12 months	10.4. 51	0.40	50	70	30	normal	normal	clear	very increased
	13.4. 51	0.35	25	86	14				
	18.4. 51	0.25	15	85	15				
	23.4. 51	0.20	12	87	13				normal

examination of smears of the cerebrospinal fluid and cultures were negative both for the Koch bacillus and other organisms. Wassermann and Mantoux tests were negative too.

Of course, it would have been a more scientific procedure if, in conjunction with the lumbar punctures and the above laboratory examinations, investigations had been undertaken to ascertain whether the causative factor of the polymorphous epidemic of poliomyelitis and, espccially in the third category cases, the causative agent were one of the known types of poliomyelitic virus, i.e. Brunhilde, Lansing, Leon or Coxsackie virus.

As to the last virus, one must be extremely circumspect since it has been proved that it affects human muscles and gives rise to paralysis similar to that of poliomyelitis. But since different groups and types of Coxsackie viruses have been isolated formerly from cases of poliomyelitis vera, and later on from cases with various febrile states of unknown etiology, namely, myalgias, pleurodynias or the so-called estival influenza and finally from healthy carriers, the problem of diagnosis of these diseases and the role of Coxsackie virus as a causative agent has been complicated even more.

Moreover, we must confess that the laboratory examination for poliomyelitis and Coxsackie viruses is unfortunately up to the present unrealisable in our country because of lack of necessary means.

One case of poliomyelitis affecting collectively inpatients at a nursery in Switzerland is reported by Swiss doctors.

Cases of a latent form of poliomyelitis are reported by AYCOCK and KRAMER (1930) and TURNER, YOUNG and MAXWELL (1945) who established the presence of antipoliomyelitis antibodies in the blood serum of individuals who had never been ill from poliomyelitis. The former authors detected them in healthy adults (85–95 per cent) dwelling in regions where poliomyelitis had broken out, and the latter, among healthy children from 0–14 years old.

MOLLARET asserts that not only do there exist forms of latent poliomyelitis which he calls "unapparent" forms but, also, they are more frequently encountered than the other poliomyelitic forms during the epidemics. He further asserts that these forms are latent intestinal poliomyelitic infections, due to the enterotropic virus of poliomyelitis (MOLLARET).

Summary

The scientific interest roused from the study of the epidemic of poliomyelitis that broke out in the Foundlings Asylum of Athens shows that the disease caused a great morbidity, by the mere fact that 26 out of 250 infants have been affected; it revealed a polymorphous clinical picture; and worthy of note is the latent form of the poliomyelitic infection of the nervous system. There is evidence to show that during the epidemic of poliomyelitis, apart from the latent forms of intestinal poliomyelitic infection reported by MOLLARET, there is also a latent form of poliomyelitic infection of the nervous system, without paralysis, fever or any other clinical manifestation, being revealed only by the well-known findings of poliomyelitis in the cerebrospinal fluid. We have been unable to find similar cases to those of the third category in the available bibliography.

Remarques à propos d'une épidémie de poliomyélite.

Au cours d'une épidémie à Athènes, une forme latente de la maladie a été observée. On pouvait noter l'absence de paralysies, de fièvre ou de tout autre manifestation clinique. Elle se traduisait seulement par les signes bien connus de la poliomyélite dans le liquide céphalo-rachidien.

Bemerkungen zu einer Poliomyelitisepidemie.

Während einer Poliomyelitisepidemie in Athen wurde eine latente Form der Krankheit beobachtet, die ohne Lähmung, Fieber oder andere klinische Manifestationen auftrat und nur durch die wohlbekannten poliomyelitischen Liquorbefunde aufgedeckt wurde.

Constataciones en una epidemia de poliomyelitis.

En una epidemia de poliomielitis en Atenas se observó una forma latente de la enfermedad, sin parálisis, ni fiebre, ni ninguna otra manifestación clínica. Solo se comprobó las manifestaciones del líquido céfalo raquídeo.

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Active Basal Immunity and Its Application to Epidemiology

III. Combined Immunization against Diphtheria, Tetanus, and Pertussis in Infancy

by BO VAHLQUIST, LENNART HESSELVIK and HANS ERICSSON

Several investigations in recent years have shown that the infant is much more capable of forming antibodies against various diseases than was earlier supposed. It has further been proved that several antigens may be combined into one vaccine without risk of a reduction of their antibody-producing capacities. These two facts may be said to form the foundation of the different schemes of combined immunization during infancy which have been suggested and practised by various workers (DI SANT' AGNESE, PETERSON and CHRISTIE). In the following pages some practical aspects of such immunizations will be discussed. For a general survey of the subject the reader is referred to LAPIN.

Our vaccination scheme comprises inoculation against diphtheria, tetanus, and pertussis. Although the first two diseases are at present very rare in Sweden, it has been deemed desirable, particularly as a precautionary measure, to confer on the child population a basal immunity against them (*vide* the two foregoing papers in this issue). Vaccination against pertussis is aimed at diminishing the risk of contracting this disease in infancy and/or of modifying its course should it appear.

Material

The children were selected from those regularly attending the infant welfare centre at the Pediatric Clinic of Uppsala. They were all less than one year old.

The triple vaccine (diphtheria, tetanus, pertussis) was manufactured by the Swedish State Bacteriological Laboratory. Two different preparations were tested. Both contained 12.5 flocculation units of diphtheria toxoid and 7.5 of tetanus toxoid per ml, but vaccine I contained 15 billions and vaccine II 20–25 billions of pertussis micro-organisms per ml.

The local anaesthetic, xylocain, was added as described by HESSELVIK and ERICSSON. The vaccine was given in a standard dose of 1 ml. It was injected, when not otherwise stated, deep into the subcutaneous tissue of the supraspinous fossa.

Experimental Observations

The first inoculation of a combined vaccine against diphtheria, tetanus, and pertussis (triple vaccine) is given at the age of three months, at which time the passive immunity which might possibly have been conveyed to the child during its intra-uterine life should have expired. The subsequent injections are given at 4 1/2 and 6 months, respectively, these being the intervals which fit in best with the infant welfare centre visits. The full immunization schedule, including BCG and smallpox vaccinations, is as follows:

neonatal period	BCG vaccination
3 months	triple vaccine
	tuberculin test
4 1/2 months	triple vaccine
	smallpox vaccination
6 months	triple vaccine
	check of smallpox vaccination.

General Reactions

To estimate the extent to which generalized reactions occur in connection with triple immunization, the rectal temperature was measured in 64 infants in the evening of the day of vaccination and in the morning and evening of the following day. Fourteen, i.e. 22 per cent, showed a temperature of 38°C or more, but none as high as 39°. The temperature invariably fell again within 36 hours of the inoculation. The febrile reactions may therefore be regarded as very moderate.

Local Reactions

The appearance of a rather tender infiltration at the site of the injection is common. In most instances the infiltration subsides within a few days. Sometimes, however, it persists and may finally lead to the formation of a sterile abscess. A persisting, indolent nodule is quite a common and normal occurrence.

The frequency of this infiltration was studied in 144 infants inoculated with the triple vaccine I, and in 50 after injection of vaccine II. The size of the infiltration was measured after 3 days and after 6 weeks (Table 1).

TABLE 1

Local reactions evoked by two types of triple vaccine.

	Percentage of children showing:			
	No infiltration	Infiltration-diameter		
		< 10 mm	10–20 mm	> 20 mm
After 3 days				
Vaccine I	32	39	24	5
Vaccine II	20	32	30	18
After 6 weeks				
Vaccine I	97	3	0	0
Vaccine II	66	26	8	0

It is seen that vaccine I, with its lower content of pertussis bacilli, gave rise to a moderate number of transient infiltrations and a quite insignificant number of persistent ones. Vaccine II, having a stronger pertussis component, produced considerably more infiltrations, particularly of the persistent type. This tallies with the fact that the injection of vaccine I in more than 500 children was in no case followed by a sterile abscess, whereas vaccine II caused such abscesses in about 0.7 per cent of 1,500 infants.

Site of Inoculation

As mentioned above, the inoculations were generally given in the supraspinous fossa. This site was selected because it seemed probable that the loose subcutaneous tissue there would receive the relatively large volume

TABLE 2

Local reactions evoked in different skin sites by triple vaccine.

	Percentage of children showing:			
	No infiltration	Infiltration-diameter		
		< 10 mm	10–20 mm	> 20 mm
After 3 days				
Arm	8	28	42	22
Leg	4	16	54	26
Back	20	32	30	18
After 6 weeks				
Arm	48	37	15	0
Leg	42	42	16	0
Back	66	26	8	0

TABLE 3

Degree of discomfort experienced during first 24 post-injection hours by the children comprised by Table 2.

	Percentage of children showing:		
	No discomfort	Slight discomfort	Considerable discomfort
Arm	58	34	8
Leg	66	28	6
Back	40	52	8

of vaccine fluid without distressing local reactions. A comparison was made, however, between the local effects of injections there and in two other common sites, namely, the deltoid region of the arm and the lateral aspect of the thigh. One hundred and fifty children were divided into 3 groups and inoculated with vaccine II in the arm, leg, and back, respectively. The infiltrations evoked were measured after 3 days and after 6 weeks and the degree of discomfort experienced by the children during the first 24 hours recorded by home visitors (Tables 2 and 3).

The results apparently point to a smaller risk of infiltration, particularly of the persistent type, in the supraspinous fossa than in the arm or the leg. This should certainly be considered more important than the finding that inoculation in the back seems to cause rather greater discomfort.

Serological Response to Immunization with Triple Vaccine

Diphtheria.—The antitoxin titres against diphtheria obtained with 3 consecutive injections of the triple vaccines (all having the same toxoid content) might, considering the efficacy of repeated, properly spaced injections, be expected to be high. Six weeks after the completed course of injections the titres of diphtheria antitoxin were determined in 22 infants. All showed values higher than 0.1 I.U./ml.

Thus, immediately after the series of injections the children all possessed the immunity deemed desirable for actual protection. Comparison with the results of earlier work (ERICSSON and HESSELVIK) shows for certain that basal immunity lasting for at least 5 years was achieved.

Tetanus.—The tetanus antitoxin titre was determined by a micromethod using mice (ERICSSON). In all of 22 tested children the titre was higher than 0.1 I.U. This value is generally accepted as corresponding to a reliable immunity against tetanus.

As shown in an earlier study (ERICSSON), and discussed in the introduction to this series of publications, the principle of basal immunity and booster

TABLE 4

Antipertussis agglutinin titres obtained with two types of vaccine.

Agglutinin titres	Number of infants	
	Vaccine I	Vaccine II
1/5120	—	2
1/2560	—	—
1/1280	—	—
1/640	1	—
1/320	2	6
1/160	2	3
1/80	2	2
1/40	2	4
1/20	2	1
1/10	1	—
0	5	1
Total	17	19

dose which is of undoubted importance in diphtheria may also be applied to tetanus. The basal immunity, determined as the antitoxin titre, achieved with a series of triple vaccinations compares very favourably with corresponding titrations after a single injection of a large amount of antigen (ERICSSON). Since single-injection immunization has been proved to produce satisfactory results, equivalent or better results are indisputably achieved by the scheme of triple vaccination.

Pertussis.—In order to obtain an estimate of the result of the immunizations against pertussis the relevant agglutinins were titrated in blood from 2 series of infants who, 8 weeks previously, had completed a full course of inoculations with vaccines I and II, respectively (Table 4).

It seems clear that the response to vaccine I was unsatisfactory. A large proportion of the infants showed no or very weak serological reactions to immunization with this vaccine, i.e. with a total of 45 billion pertussis bacteria. On the other hand, a course of vaccine II, with altogether 60 to 75 billion pertussis bacilli, had a considerably stronger effect. More than half of the immunized children had agglutinin titres of or exceeding 1/160.

Summary

Some practical aspects of simultaneous immunization of infants against diphtheria, tetanus, and pertussis by means of mixed (triple) vaccines were investigated. Three injections were made, at 3, 4 $^1/_2$, and 6 months of age. Mild febrile reactions occurred in 22 per cent of the infants. Local reactions were common, particularly when a vaccine with a stronger pertussis component was employed. Three different sites of inoc-

ulation (back, arm, and leg) were compared; preference is given to the supraspinous fossa since persistent infiltration with consequent risk of abscess was less common there. The antibody response to diphtheria and tetanus was very satisfactory. In regard to pertussis, vaccine I (45 billion pertussis bacilli per 3 cc) gave rather low agglutinin titres, whereas vaccine II (60–75 billions per 3 cc) evoked a more satisfactory response.

Immunité basale active et ses applications à l'épidémiologie. III. Immunisation associée contre la diphtérie, le tétanos et la coqueluche chez l'enfant.

Quelques aspects pratiques de la vaccination triple associée (DTC) de l'enfant sont envisagés. Trois injections furent faites respectivement à 3, 4 $^1/_2$ et 6 mois d'âge. Dans 22 % des cas on observa une légère réaction fébrile. Une réaction locale est habituelle en particulier en cas de vaccination avec une dose forte de toxine coquelucheuse. On compara trois sièges d'inoculation différents: dos, bras et jambe. La préférence est donnée à la fosse sus-épineuse pour laquelle les risques d'infiltration persistante avec comme conséquence un abcès sont moins grands. La réponse des anticorps vis à vis de la diphtérie et du tétanos fut très satisfaisante. En ce qui concerne la coqueluche, le vaccin I (45 billions de bacilles pour 3 cc) donna des titres d'agglutinines plutôt bas, tandis que le vaccin II (60–75 billions pour 3 cc) donna une réponse bien meilleure.

Aktive Basisimmunität und ihre Bedeutung für die Epidemiologie. III. Kombinierte Immunisierung gegen Diphtherie, Tetanus und Pertussis im Säuglingsalter.

Einige praktische Aspekte der gleichzeitigen Impfung von Kindern gegen Diphtherie, Tetanus und Pertussis durch gemischte (dreifache) Vaccine werden untersucht. Ausgeführt werden 3 Injektionen im Alter von 3, 4 $^1/_2$ und 6 Monaten. Milde Fieberreaktionen traten bei 22 % der Säuglinge auf. Gewöhnlich kam es zu lokalen Reaktionen, hauptsächlich, wenn eine Vaccine mit stärkerer Pertussiskomponente verwendet wurde. Drei verschiedene Impfstellen (Rücken, Arm und Bein) wurden verglichen. Der Vorzug wird der fossa supraspinosa eingeräumt, weil die bestehende Infiltration hier weniger zur Abszessbildung neigt. Die Antikörperreaktion gegen Diphtherie und Tetanus war sehr zufriedenstellend. In Bezug auf Pertussis gab das Vaccin I (45 Billionen Pertussisbazillen auf 3 ccm) sehr niedrige Agglutinintiter, wogegen das Vaccin II (60–75 Billionen auf 3 ccm) eine mehr befriedigende Reaktion hervorrief.

Inmunidad básica activa y su aplicación a la epidemiología. III. Inmunización combinada contra la difteria, el tétanos y la tosferina en la infancia.

Se han investigado algunos aspectos prácticos de inmunización simultánea de niños contra la difteria, el tétanos y la tosferina por medio de vacunas mezcladas (triples). Se pusieron tres inyecciones, la edad de los niños era de 3, 4 $^1/_2$ y 6 meses. Se presentaron reacciones de fiebre leves en un 22 por ciento de los niños. Fueron comunes las reacciones locales, particularmente al usar una vacuna con el componente de la tosferina más fuerte. Se compararon tres distintos sitios de inoculación (la espalda, el brazo y la pierna) dándose la preferencia a la fosa supraespinal, en donde el consiguiente riesgo de abceso fué menos común que en los demás sitios. La respuesta de anticuerpo a la difteria y al tétanos fué muy satisfactoria. Por lo que respecta a la tosferina, la vacuna I (45 billiones de pertussis bacilli por 3 cc) dió títulos bastante bajos, mientras la vacuna II (60–75 billiones por 3 cc) produjo una respuesta mas satisfactoria.

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Active Basal Immunity and Its Application to Epidemiology

IV. Initial Pain in Diphtheria-Tetanus-Pertussis Vaccination

by LENNART HESSELVIK and HANS ERICSSON

The unpleasant side effects most commonly encountered when using absorbed purified diphtheria vaccine for mass inoculation may be said to comprise:

A. General reactions, mainly manifested as fever, joint pains, malaise, and, occasionally, rash.

B. Local reactions, which may be further classified as

1. Initial pain, occurring immediately after the injection and reaching its peak within a few minutes. This pain is due partly to the mechanical distension caused by the injected fluid, but mainly to some unknown factor in the vaccine which it has not yet been possible to eliminate (ERICSSON). Our experience of the properties of vaccine produced by foreign manufacturers is, however, limited.

2. Late pain during the first two days following the injection, due to a local inflammatory reaction and associated with the formation of a tender infiltration. This reaction may be ascribed to the injection of a foreign protein adsorbed onto a mineral vehicle.

3. Persistent, indolent infiltration forming a subcutaneous nodule may be regarded as a normal sequel of the injection of an absorbed vaccine.

4. A sterile subcutaneous abscess may in some cases be the final result of the local reaction.

The most serious side reactions are ascribed to hypersensitivity to a specific component of the vaccine (PAPPENHEIMER *et al.*), and are generally observed in adults. They impose very strict limits on the use of this type of vaccine for adult immunization. In children such reactions, especially of the generalized type, are much less severe. But with combinations of different antigens, e.g. diphtheria and tetanus or diphtheria, tetanus, and pertussis, all forms of side reaction may be intensified. Any measure which may diminish their severity should therefore be considered.

In pediatric practice the initial pain is an important side effect. The obvious discomfort of the child immediately after inoculation is distressing both to mothers and doctors. In infant welfare clinics, with many children present at one time, considerable inconvenience may easily result. When large-scale immunization with the aim of conferring basal immunity is contemplated as a regular part of an infant welfare programme, the problem of initial pain merits special attention. It is self-evident that the specific action of the vaccine must not be diminished by the measures taken to reduce the side reactions.

Material

The discovery of a local anaesthetic with particularly rapid action—xylocain, Astra, or diethylaminoaceto-2, 6-xylidide (WIEDLING)—seemed to provide the possibility of reducing the initial pain in diphtheria immunization. The addition of xylocain to the suspension of diphtheria toxoid was originally suggested by BLUME. We use xylocain in a final concentration of 0.33 per cent with the aluminum-precipitated diphtheria toxoid prepared at the Swedish State Bacteriological Laboratory according to the method described by ERICSSON (1946). The same method is used for the preparation of tetanus vaccine (ERICSSON).

The diphtheria-tetanus-pertussis (triple) vaccine is prepared by mixing the precipitated toxoids with pertussis vaccine produced on fluid synthetic medium according to the method of COHEN and WHEELER as adopted by ARVIDSON and ULLBERG-OLSSON.

The content of antigen per ml for diphtheria-tetanus vaccine is 50 Lf of diphtheria toxoid and 30 Lf of tetanus toxoid, and for triple vaccine 12.5 Lf of diphtheria toxoid, 7.5 Lf of tetanus toxoid and 15 billions of pertussis bacteria. The diphtheria-tetanus vaccine contains 1 mg of aluminum as $ALPO_4$ per ml and the triple vaccine half this amount.

Experimental

Since xylocain is well known for its stability and lack of reactivity it was considered very probable that it could be added to the vaccine during the process of manufacture without risk of damage to the vaccine or diminution of the analgetic effect, even if the preparation was stored for the generally accepted period of one year. The immunological activity and the analgetic effect, however, were checked by special experiments.

To some vials of a batch of diphtheria vaccine xylocain was added. Immediately, and after 1/2, 1, 2, 4, 6, 12, and 24 months, 50 Lf of the preparation were injected into guinea pigs. The titre of antitoxin 6 weeks after each injection was compared with the titre obtained by injection at the same

TABLE 1

The analgetic effect of xylocain added to diphtheria toxoid.

	Number of persons injected	
	Immediately after the addition of xylocain	One and a half years after the addition of xylocain
During and immediately after injection		
Less pain with xylocain	8	
No difference	5	
More pain with xylocain	0	
Three minutes after injection		
Less pain with xylocain	12	10
No difference	1	0
More pain with xylocain	0	0

time of the same quantity of antigen without added xylocain. No difference was ever observed between the effect of the preparation to which xylocain had been added and that of the control injection.

In order to test the analgetic effect of the added xylocain the following experiment was carried out. From a batch of diphtheria-tetanus vaccine two vials were taken. To one was added xylocain and the other was left intact. Thirteen volunteers (medical students and nurses) received injections from both vials; the two subcutaneous injections, each of 0.5 ml, were performed in immediate succession into symmetrical sites over the deltoid regions. The pain experienced during and immediately after the injections was noted (Table 1). The experiments were so arranged that neither the giver nor the recipient of the injections was aware of which syringe contained the analgetic.

Three minutes after the injections 12 of the 13 volunteers had no pain at the site of the xylocain-vaccine injection, whereas 12 had pain of varying intensity at the other site.

To determine whether storage had influenced the analgetic effect of the added xylocain, the experiment was repeated after 18 months, using the same preparation and the same technique. Ten volunteers participated.

All without exception experienced considerably less pain after three minutes at the site where the xylocain preparation had been injected than at the other site. All 10 reported pain from the injection without xylocain.

Practical experiences

It could thus be considered proved that the addition of xylocain to diphtheria toxoid gave a preparation which caused considerably less pain than one without it, and that the product thus obtained was sufficiently stable for practical use. Subsequently xylocain was added to all preparations of diphtheria-tetanus toxoid and triple vaccine used at the pediatric immunization clinic in Uppsala. The superiority of the xylocain preparations was obvious. Several thousand injections were given and the patients, mostly infants, evidently had little or no pain a few seconds after the injection. At subsequent visits to the immunization clinic it was clear that the children did not as a rule retain the usual unpleasant memory of their previous experience.

The addition of xylocain has also been adopted for tetanus vaccine at the out-patient department of the surgical clinic at the Karolinska Hospital, and its use has met with success.

Summary

The addition of a quick-acting local anaesthetic (xylocain, Astra) to aluminum-precipitated diphtheria and tetanus toxoid and to triple vaccine (diphtheria-tetanus-pertussis) was tested in human subjects. A considerable reduction of the initial pain following the injection was noted. No diminution of the immunizing effect was observed in animal experiments.

Immunité basale active et ses applications à l'épidémiologie. IV. Douleur initiale lors de la vaccination D.T.C.

L'addition d'un anesthésique local à action immédiate (Xylocaine, ASTRA) au précipité aluminique de toxoïde diphtérique et tétanique et de même au vaccin triple associé (DTC) a été essayée chez l'homme. Une réduction considérable de la douleur locale suivant l'injection fut constatée, sans réduction du pouvoir immunisant (ceci chez les animaux en expérience).

Aktive Basisimmunität und ihre Bedeutung für die Epidemiologie. IV. Anfänglicher Schmerz bei Diphtherie-Tetanus-Pertussis-Impfung.

Die Zugabe eines rasch wirksamen lokalen Anästheticums (Xylocain, ASTRA) zum Aluminiumpräzipitat des Diphtherie- und Tetanustoxoids und zum Dreifach-Impfstoff (Diphtherie-Tetanus-Pertussis) wurde beim Menschen geprüft. Eine beträchtliche Verminderung des der Injektion folgenden initialen Schmerzes wurde festgestellt. Im Tierexperiment wurde keine Herabsetzung des immunisierenden Effektes beobachtet.

Inmunidad básica activa y su aplicación a la epidemiología. IV. Dolor inicial en la vacuna de la difteria-tétanos-tosferina.

La adición de un anestético local de actuación rápida (xylocain, ASTRA) al precipitado de aluminio del toxoide de la difteria y el tétanos y de la vacuna triple (difteria-tétanos-tosferina) fué probada en sujetos humanos. Se notó una reducción considerable del dolor inicial que sigue a la inyección. En la experimentación animal no se observó ninguna disminución del efecto de immunización.

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Comparison of the Action of Vitamin K_1 with that of Synkavit in the Newborn

by HOLGER V. DYGGVE, HENRIK DAM, and EBBE SØNDERGAARD

Several investigators (SHOSKES *et al.*, WATKIN *et al.*, and others) have shown the marked superiority of vitamin K_1 over menadione and synkavit in counteracting the effect of dicoumarol and similar anticoagulants on the prothrombin time of experimental animals and adult patients. Recently it has also been shown (DAM and SØNDERGAARD) that vitamin K_1 injected intravenously acts much faster than menadione and synkavit on the prothrombin time of vitamin K-deficient chicks.

It would, therefore, be of interest to investigate whether a similar difference between the two forms of vitamin K can also be found in the newborn.

Experimental

The tests were carried out with normal, full term infants 2 to 3 days after birth. Infants with varying degrees of prolonged prothrombin time were selected for the study.

Vitamin K_1 was given as a sterile transparent aqueous colloidal 1% solution with polyoxyethylene-sorbitan-monooleate as association colloid (the same kind of solution as had been used previously in experiments with chicks). Synkavit[2] (tetrasodium salt of 2-methyl-1,4-naphthohydroquinone-biphosphate) was given as a sterile 1% aqueous solution obtained directly from the manufacturer.

Prothrombin times were determined immediately before and at various intervals after the intravenous injection of the substances to be tested. The method was that of LARSEN and PLUM using capillary blood and thromboplastin prepared from human brain without acetone extraction or drying (DAM and GLAVIND).

The following doses were tested:

Vitamin K_1	10 mg	intravenously
»	0.1mg	»
»	10 mg	orally
Synkavit	10 mg	intravenously
»	0.1 mg	»
»	10 mg	orally.

[1] We wish to thank Professor E. RYDBERG for permission to carry out this study in his department.

[2] Synkavit and Ephynal used in these studies were kindly placed at our disposal by F. Hoffmann-la Roche & Co., A. G., Basle.

Results

The results are shown in Figures 1 and 2.

Some more cases were examined but since they gave results falling within the ranges shown, they were not plotted in the graphs.

The prothrombin time for normal adults was 18–19 sec.

The values obtained 18 hours after injection (or oral ingestion) lay between 33 and 64 sec. except for 0.1 mg synkavit, in which case the values after 18 hours were more scattered (from 45 to 103 seconds).

It is evident that there is no *marked* difference between vitamin K_1 and synkavit with respect to the velocity of the fall in prothrombin time.

When given orally, both compounds act more slowly than when injected intravenously.

Of the infants given 10 mg K_1 orally, one had an initial prothrombin time of 1800 sec. In this case the prothrombin time decreased as follows:

0 h	1800 sec.	4 h	111 sec.
1 »	1002 »	19 »	64 »
2 »	333 »	43 »	40 »
3 »	145 »	66 »	30 »

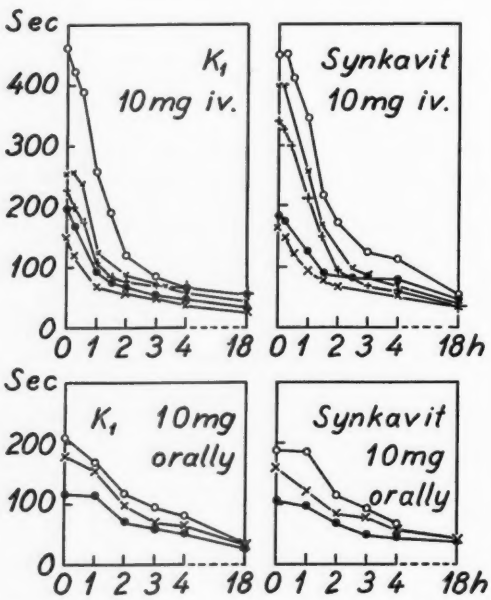

Fig. 1. Ordinate: Prothrombin time in seconds. Abscissa: Hours after administration. iv. = intravenously.

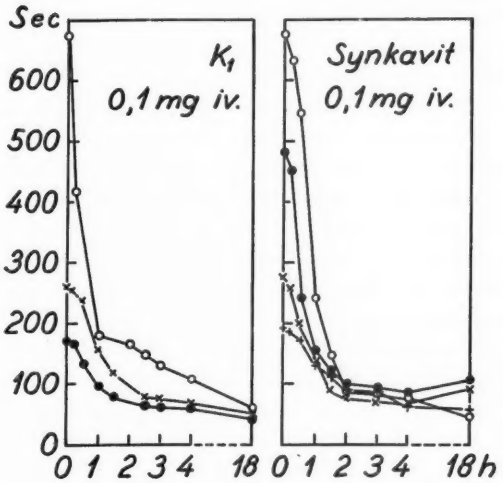

Fig. 2. Ordinate: Prothrombin time in seconds. Abscissa: Hours after administration. iv. = intravenously.

Doses of 0.1 mg vitamin K_1 or synkavit (intravenously) acted as fast as doses of 10 mg of the same substances, but in some cases receiving 0.1 mg of synkavit the prothrombin times rose somewhat in the interval between 4 and 18 hours after the injection.

In all cases, the velocity of action of vitamin K_1 and synkavit was much slower in infants than found previously in vitamin K-deficient chicks even for synkavit.

Discussion

It is not possible at present to explain why in the newborn there is no marked difference between the action of vitamin K_1 and of synkavit or why these substances act more slowly in the newborn than in vitamin K deficient chicks.

The same applies to the fact that it takes about 6–12 months for the prothrombin time of infants to reach the value for normal adults.

An analysis of the individual plasma coagulation factors and their variation after birth seems necessary for the deeper understanding of these facts.

Another approach to the problem would be the consideration whether other dietary deficiencies than that of vitamin K limit the capacity of the blood clotting system in the infant. In this respect it might be of interest to recall that besides vitamin K, vitamin E is also low in the newborn (MINKOWSKI; WRIGHT, FILER and MASON; GYORGY, COGAN and ROSE). Therefore, we have given to 4 infants of 1 to 2 days of age 1 dose of 50 mg *d, l*-α-

tocopherol acetate (Ephynal, Roche) orally in sugar-water. Twenty-four hours later the prothrombin times were 235, 248, 358, and 740 sec., respectively. Immediately after the determination of the prothrombin times each of the infants was given an intravenous injection of 10 mg vitamin K_1. Thereafter the prothrombin times were determined at the same intervals as in the experiments in which no vitamin E was given. The decline in prothrombin time was found to be within the range found for infants not receiving *d,l*-α-tocopherol acetate.

It seems worthwhile to point out that according to our experience as well as that of most other investigators, infants and dicoumarol-treated patients can tolerate a more prolonged prothrombin time without showing hemorrhages than is the case in chicks. The reason for this may be related to the fact that contrary to what is the case in birds, blood platelets play a considerable role in initiating coagulation in mammals.

Summary

In newborn infants with varying degrees of prolonged prothrombin time no marked difference could be found between the velocity of action of vitamin K_1 (10 or 0.1 mg) or synkavit (10 or 0.1 mg) when administered intravenously. This was also the case when the two substances were given orally (10 mg). The result is in contrast to the known superiority of vitamin K_1 in vitamin K deficient chicks and in dicoumarol-treated chicks or patients. Intravenous injection of vitamin K_1 as well as of synkavit acts more slowly in infants than in chicks. Ingestion of *d,l*-α-tocopherol acetate (50 mg) to infants 24 hours before the injection of vitamin K_1 did not result in a more rapid action of the latter substance.

Comparaison de l'action de la vitamine K_1 et du synkavit, chez le nouveau-né.

Chez les nouveau-nés, présentant des temps de prothrombine plus ou moins longs, nous n'avons pas trouvé de difference notable en ce qui concerne la rapidité d'action de la vitamine K_1 (10 ou 0,1 mg) et celle du synkavit (10 ou 0,1 mg) après injection intra-veineuse. Il en était de même lorsque ces substances étaient administrées par voie orale (10 mg). Ce résultat n'est pas conforme avec la supériorité établie de la vitamine K_1 chez les poulets en carence de vitamine K et chez les poulets ou les êtres humains traités par le dicoumarol. Les injections intra-veineuses de la vitamine K_1, aussi bien que de la synkavit ont un effet plus lent chez les nouveau-nés que chez les poulets. L'ingestion de 50 mg de l'acetate de *d,l*-α-tocopherol à des nouveau-nés, 24 heures avant l'injection de la vitamine K_1, n'entraîne pas d'action plus rapide de cette dernière substance.

Vergleich der Wirkung von Vitamin K_1 mit derjenigen von Synkavit beim Neugeborenen.

Bei Neugeborenen mit verschiedenen Graden von prolongierter Prothrombinzeit konnten bei intravenöser Anwendung keine deutlichen Unterschiede zwischen der Wirkungsintensität von Vitamin K_1 (10 oder 0,1 mg) oder Synkavit (10 oder 0,1 mg) gefunden werden. Dies war auch der Fall, wenn beide Substanzen peroral (10 mg) verabreicht wurden. Dieses Ergebnis ist abweichend von der früher gefundenen

Überlegenheit des Vitamins K_1 bei Hühnchen mit Vitamin-K-Mangel und bei mit Dicoumarol behandelten Hühnchen oder Patienten. Intravenöse Injektion von Vitamin K_1, sowie von Synkavit, wirkt bei Kindern langsamer als bei Hühnchen. Führt man den Kindern 24 Std. vor der Injektion von Vitamin K_1, *d,l*-α-Tocopherol zu, resultiert daraus keine raschere Wirkungsweise des Vitamins.

Comparación de la acción de la vitamina K_1 con el «Synkavit» en el recién nacido.

En niños recién nacidos con distintos grados de prolongación del tiempo de protrombina, no pudo encontrarse una clara diferencia entre la velocidad de acción de la vitamina K_1 (10 o 0,1 mg) o el «Synkavit» (10 o 0,1 mg) si se administra por vía intravenosa. Este también fué el caso cuando se dieron las dos substancias por vía oral (10 mg). Este resultado contrasta con la conocida superioridad de la vitamina K_1 en polluelos que sufrían de carencia en vitamina K y en polluelos o pacientes tratados con dicumarol. Inyección intravenosa de vitamina K_1 así como de «Synkavit» tiene una acción más lenta en niños que en polluelos. La ingestión de acetato de *d,l*-α-tocoferol (50 mg) a niños 24 horas antes de la inyección de vitamina K_1 no hizo que la acción de la última substancia fuera más rápida.

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Penicillin Treatment of Scarlet Fever[1]

by JUSTUS STRÖM

FLEMING, in his book "Penicillin" (1946), pointed out the great sensitivity to penicillin of the hemolytic streptococci, and also stated that bacterial complications in cases of scarlatina can be greatly reduced by this antibiotic. He considers, however, that an antitoxic serum is still required, since penicillin has no direct action on toxins.

Quite a large number of investigations have been carried out during the last five years, both in the U.S.A. and in European countries (cf. bibliography), concerning the effect of penicillin on scarlatina. Most authors appear to consider penicillin the drug of choice. Others, however, are less enthusiastic, and to judge from certain textbooks and handbooks there is still some doubt. Thus, MUSSER points out in Pullen's "Communicable Diseases" (1950) that penicillin has been recommended, but points to the lack of control tests. STANLEY BANKS (1951) considers specific treatment unnecessary in the mild cases that are now so usual, and in more severe cases he recommends antitoxin with or without an appropriate antibiotic.

Since 1946 systematic investigations have been conducted at the Stockholm Hospital for Contagious Diseases, and the results are now available from test series comprising about 6,500 cases.

The various methods of test procedure adopted at different periods are illustrated in the Table. As will be seen, the treatment has been varied in a number of ways in respect to the number of penicillin administrations per day, the method of administration—by injection or perorally—and the day of its commencement. As a rule treatment has been continued until 3 negative tests for hemolytic streptococci were obtained, but not less than 6 days. The methods of hospitalization have been varied; thus in the control series I-K the patients were kept in isolated rooms. The period of hospitalization has been reduced from the 6 weeks that was previously usual to 1 week during the epidemic period 1949–1951. Moreover, during the latter period the tests

[1] This investigation was supported by grants from the Town of Stockholm and AB KABI Stockholm.

TABLE 1

Frequency of Complications in Different Test Series

Test period	Year	Series	Treatment				Hosp. weeks	Number scarl. cases	Complications							
			From day	Times per day	Admin. inj. = i p. os = o	Days			Synovitis	Myocard.	Nephritis	Lymphadenit	Otitis	Peritons.	Sinusitis	Paronych. Impetigo
a.	1946—47	Ka	—	—	—	—	6	228	3.5	3.2	0.9	30.7	10.5	1.8	1.8	8.7
	1946—47	Pa	2	8	i	6	6	221	2.7	2.2	0.4	2.2	—	—	0.4	4.5
b.	1947—48	I-K	—	—	—	—	3	219	2.7	6.4	0.5	13.7	3.2	1.4	0.9	11.9
	1947—48	Pb_2	2	7, 3, 2	i	6	3	222	2.3	2.3	0.5	5.9	1.8	—	2.3	2.3
	1947—48	Pb_3	5	7, 3, 2	i	6	3	211	3.3	5.7	—	5.7	2.4	—	0.5	5.2
c.	1948—49	Pci	2	1	i	6	3	260	0.8	4.1	—	4.6	0.8	—	0.4	3.5
	1948—49	Pco	2	3	o	6	3	255	—	3.5	—	10.6	0.8	—	2.4	3.1
d.	1949	Pdi	2	1	i	6	1	1 669	0.4	2.1	0.1	10.4	1.6	0.3	0.9	10.4
e.	1950—51	Pei	2	1	i	6	1	2 148	0.3	1.8	0.1	8.9	(2.7)*	0.3	1.8	9.5
	1950—51	Pco	2	3	o	6	1	1 029	0.3	2.0	0.5	12.2	(1.0)*	0.2	3.0	11.0

Test periods a, b and c: solely cases without initial complication
d and c: all cases

K = control cases. — I-K = isolated control cases (separate rooms)

P = penicillin cases: Numerals 2 and 5 = day when treatment commenced
Letters i and o = penicillin injection and per os.

* Otitis in series e: cases treated from start by penicillin injection.

comprise all cases, while earlier series comprised only those cases which were initially uncomplicated.

As regards the dosage of penicillin, the following amounts were given at different periods. The dose was increased uniformly in groups 1–4, 5–9, 10–14 and above 15 years.

Test period	Dose
a	5,000– 20,000 IU × 8 (inj.)
b	20,000– 80,000 IU × 7, later × 3 and 40,000–100,000 IU × 2 (inj.)
c, d, e	100,000–200,000 IU × 1 (inj.—pen.-procaine); 75,000–150,000 IU × 3 (per os—ser. Pco amorph. pen, ser. Peo pen.-procaine)

In test series *a*, the period of hospitalization was the hitherto usual one, i.e. 6 weeks. *Both treated and untreated were placed in general wards.* The control series Ka shows the high frequency of complications to which we were previously accustomed. In the comparative series Pa, in which the cases were treated with 8 penicillin injections a day for 6 days, the complications are greatly diminished. Otitis has not occurred at all (10.5 per cent in Ka), lymphadenitis decreased to one-fifteenth, peritonsillitis is lacking and sinusitis was reduced to nearly one-fifth. The toxic complications (synovitis, myocarditis, nephritis) have also been less frequent in the penicillin series, but no statistically reliable differences exist.

It is known from many investigations—and, for example, from the Stockholm Hospital for Contagious Diseases through the works of LICHTENSTEIN and EHINGER—that some complications are connected with cross-infections in the wards. Often these complications are due to a new type of hemolytic streptococcus coming from another patient (EHINGER).

Since it appeared to be of interest to discover the significance of these cross-infections, and to see whether it was possible to reach as low a complication frequency as in penicillin-treated cases if the cross-infections were eliminated, comparative tests were carried out during period *b* between *isolated patients placed in separate rooms and penicillin-treated patients placed in wards.* The period of hospitalization was here 3 weeks. The isolated control cases (I-K), as was expected, manifested considerably fewer bacterial complications than the control cases in the first series (Ka). In comparison, however, with the penicillin series Pb 2 and Pb 5 (cases treated from the 2nd and 5th days respectively), there was a greater occurrence of otitis, peritonsillitis, lymphadenitis and impetigo among the isolated controls. The frequency of myocarditis was also higher in I-K than in Pb 2. By delaying treatment until the fifth day the complications increased somewhat in comparison with patients treated from the second day.

As penicillin does not need to attain a particularly high concentration in serum to combat the hemolytic streptococci effectively, it can be given per os. In period *c* a comparison was made between the complication frequencies in *patients treated by injection* (Pci) *and per os* (Pco). The difference was not significant. Those treated perorally had a somewhat higher frequency of lymphadenitis and sinusitis.

Due to the great accumulation of cases in the epidemic, prevailing during the test periods *d* and *e*, treatment had to be commenced immediately in all cases irrespective of whether complications were present or not. The only selection adopted was that, at a later stage, cases with otitis received injection treatment immediately. Every third case in period *e* was treated perorally. As will be seen from the Table, there is only a slight difference between the series in question as regards lymphadenitis and sinusitis.

It appears from these comparisons, as would be expected, that it is primarily the *bacterial complications* which can be prevented by penicillin. LEVANDER-LINDGREN, however, carried out an extensive analysis of the present material, particularly from the electrocardiographic aspect. She was able to demonstrate that the frequency of *myocarditis* also diminished as a result of penicillin treatment (LEVANDER-LINDGREN's frequency figures are included in the Table). At the same time she found that the prognosis for myocarditis in children under 15 years is as a rule very favorable, but more serious above that age.

The excellent effect of penicillin in the prevention of complications is clearly shown by this investigation. Its significance from the point of view of infection, and thereby for prophylactic treatment, is described in a separate article in this journal. The only essential weakness of penicillin treatment is a lessened immunity. Considerable light is thrown on that question by an analysis of the present material, which is presented in another publication in this journal.

Summary

From various test series during the years 1946–51 consisting of 6,500 cases of scarlatina it appears that penicillin has an excellent effect in preventing complications. Not only in comparison with normally hospitalized patients, but also with entirely isolated patients, there is a clear difference in favor of treated cases. It is also shown that the peroral therapy given was, in spite of the low dosage, very little inferior to injection from the point of view of complications. The effect in preventing complications applied particularly to the bacterial types. A difference is also apparent, however, in regard to toxic types. The only complication of this kind which proved of any significance during the years of the tests was myocarditis. According to Levander-Lindgren's investigations of the material the frequency of myocarditis also diminished as a result of penicillin treatment. This is of particular importance in patients over 15 years, in whom myocarditis is of a more serious character.

Traitement de la scarlatine par la pénicilline.

Il ressort de l'étude de 6500 cas de scarlatine répartis en plusieurs séries s'étendant de 1946 à 1951 que l'usage de la pénicilline a un effet préventif excellent sur les complications. Ceci est valable tant pour les malades hospitalisés que pour les cas traités de façon isolée. Il ressort également de cette étude que la voie orale ne se montre que très peu inférieure à la voie parentérale du point de vue des complications. L'effet préventif est en rapport en particulier avec le type bactériologique. Il existe de plus des différences si l'on considère la forme toxique. La seule complication de ce type qui ait une importance nette reste la myocardite. Selon Levander-Lindgren la fréquence elle-même de la myocardite est en régression du fait de la pénicillinothérapie. Ceci est de la plus haute importance chez les malades de plus de 15 ans pour lesquels la myocardite a un caractère plus sérieux.

Penicillinbehandlung des Scharlachs.

Aus verschiedenen Testserien während der Jahre 1946–1951 mit insgesamt 6500 Scharlachfällen geht hervor, daß Penicillin einen ausgezeichneten Effekt zur Verhinderung von Komplikationen hat. Nicht nur im Vergleich mit normal hospitalisierten, sondern auch mit vollständig isolierten Patienten ergibt sich ein klarer Unterschied zugunsten der behandelten Fälle. Es konnte gezeigt werden, daß die perorale Verabreichung trotz der niedrigen Dosierung in Hinblick auf Komplikationen der Injektion sehr geringfügig unterlegen ist. Der Effekt bezieht sich hauptsächlich auf die Verhinderung von Komplikationen bakterieller Art. Eine Differenz ist auch in Bezug auf die toxischen Typen sichtbar. Die einzige Komplikation dieser Art, welche in den Jahren der Untersuchung von Bedeutung zu sein schien, war die Myocarditis. Nach den Untersuchungen von Levander-Lindgren hat aber die Frequenz der Myocarditis infolge der Penicillinbehandlung ebenfalls abgenommen. Dies ist von besonderer Bedeutung für Patienten über 15 Jahre, bei denen die Myocarditis einen ernsteren Charakter hat.

Tratamiento de la escarlatina con penicilina.

De varias series de tests durante los años 1946–51, que consisten en 6.500 casos de escarlatina, se deduce que la penicilina tiene un efecto excelente en la prevención de complicaciones. No solamente en comparación con pacientes normalmente hospitalizados, sino también en los pacientes completamente aislados existe una clara diferencia en favor de los tratados. Tambien se ve que la terapéutica por vía oral fué, a pesar de su baja dosis, muy poco inferior a la inyección desde el punto de vista de las complicaciones. El efecto en la prevención de las complicaciones se refiere particularmente a los tipos bacterianos. También existe, empero, una clara diferencia respecto a los tipos tóxicos. La única complicacion de esta clase que demostró tener alguna importancia durante los años en que se hicieron los tests, fué la miocarditis. Concorcando con las investigaciones de Levander-Lindgren sobre el material, la frecuencia de miocarditis tambien disminuyó como resultado del tratamiento con penicilina. Esto es de importancia particular en pacientes sobre 15 años, en los cuales la miocarditis es de carácter mas serio.

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From the Hospital for Contagious Diseases, Stockholm, Sweden.
(Head: Justus Ström, M. D.)

Penicillin in the Prevention of Scarlet Fever[1]

by JUSTUS STRÖM

Hemolytic streptococci are very sensitive to penicillin. In our first attempts to treat scarlatina with penicillin we carried out quite extensive resistance tests. Out of a total of 597 tests, sensitivity to a concentration of only 0.03 IU per millimetre serum was found in 589, and to 0.06 in the remaining 8 tests.

In various test series in 1946 and 1947 on patients treated with penicillin it was shown that the streptococci had practically disappeared from the nose and throat after 3 days of treatment with 8 injections per 24 hours. The intensive therapy with numerous penicillin injections soon proved to be unnecessary. It was possible to proceed to depot penicillin with only one injection a day, and attempts were soon made with penicillin per os. LAGERCRANTZ and PETERSON (1950) demonstrated that a sufficient concentration in serum could be attained by both methods of administration. After injection, however, a satisfactory concentration was maintained for twice as long as after peroral administration. A lengthy but moderate concentration of penicillin acted better than a short but high concentration.

Once penicillin treatment has been administered, the patients no longer constituted any appreciable danger to their environment in the hospital. Thus the *recurrences*, i.e. among patients while in hospital, usually by infection from another patient, have almost disappeared. *Secondary cases among the staff* are now also very rare.

An effective combating of the hemolytic streptococci should also imply that they cannot regenerate from non-destroyed bacteria. It may be difficult, however, to get rid of them entirely. In particular, it appears that the streptococci are more liable to return in children with enlarged tonsils with tonsillar crypts or with adenoid vegetations. But it is clear that the return of bacteria is in many patients not due to the regrowth of surviving bacteria, but to infection from the environment. When patients return home after a com-

[1] This investigation was supported by grants from the town of Stockholm and AB KABI, Stockholm.

paratively short hospitalization, they often come back to an environment which still harbours hemolytic streptococci.

In parallel series in 1948 and 1949 alternate cases were treated with one injection of penicillin-procaine per day and with penicillin perorally three times a day. At least six days of treatment and three consecutive negative tests on hemolytic streptococci were required, and in addition negative tests the three last days in hospital. In spite of these similar requirements on the sanitizing effect of treatment, there proved to be a dissimilarity between the series in respect to the *return of streptococci* (STRÖM 1950). A week after discharge the streptococci had returned in 6.4 per cent of 640 injected patients and in 14.2 per cent of 640 perorally treated patients. The difference was 7.8 ± 2.1 per cent. The intensity of treatment was significant as regards the regrowth. The peroral dose had manifestly been too small. This also proved to be significant for early recrudescenses.

The most important indication of the ability of penicillin to decrease the risk of infection is, however, the occurrence of so-called *return cases*, when the patient on his return home provokes scarlatina in the environment.

The results of such an investigation are tabulated below, the return cases being indicated in different series.

In the two series from 1946–47, Ka and Pa, with 6 weeks' hospitalization, freedom from streptococci on discharge from hospital was not required. The

Return Cases

Year	Series	Hospitalization (weeks)	Hem. strept. on leaving hospital (%)		Number cases	Return Cases	
			Throat	Nose		Number	%
1946–47	Ka	6	52	37	228	10	4.4
„	Pa	6	8	7	221	2	0.9
1947–48	I-K	3	51	26	219	5	2.3
„	Pb2 + Pb5	3	0	0	433	1	0.23
1948–49	Pci	3	0	0	260	2	0.8
„	Pco	3	0	0	255	3	1.2
1949	Pdi	1	0	0	1669	5	0.30
1950–51	Pei	1	0	0	2148	3	0.13
„	Peo	1	0	0	1029	2	0.19

K = control cases.
I-K = isolated control cases.
P = penicillin cases: Numerals 2 and 5 = day when treatment commenced.
Letters i and o = penicillin injection and per os.
a–e = test periods.

control series Ka manifests a high percentage of streptococci carriers on leaving hospital, and no less than 4.4 per cent return cases. In the penicillin series Pa (5,000–20,000 IU × 8 by injection), on the other hand, only about one-sixth as many were streptococci carriers on their return home with, in consequence, only 0.9 per cent return cases. In 1947–48 a 3 weeks' hospitalization period was adopted. In the control series I-K the patients were placed in separate rooms, and in the two penicillin series Pb2 and Pb5 (treated from 2nd and 5th day, 20,000–80,000 IU × 7, followed by × 3, and finally × 2) freedom from streptococci on discharge was required. In spite of isolation and the consequent prevention of nosocomial infection, a high percentage of the patients in the I-K series were carriers of streptococci on leaving hospital, with the result that there was an occurrence of 2.3 per cent of return cases. The two penicillin series only gave rise to 0.23 per cent return cases.

In the series from 1948–49, Pci and Pco, and from 1950–51, Pei and Peo, in which freedom from streptococci was likewise required on leaving hospital, it can be seen that the difference in return cases is very slight as between patients treated by injection, Pci and Pei (100,000–200,000 IU penicillin-procaine × 1), and perorally, Pco and Peo (75,000–150,000 IU × 3). The per-oral treatment may therefore be considered to have been fully satisfactory in providing protection against infection of the environment. It is further apparent that, even during severe epidemics such as those in 1949–51, it was possible to keep the return cases down to 1–2 per mille, corresponding to one-twentieth to one-fortieth of the earlier frequency.

Thus the scarlatina patient now constitutes no appreciable danger to his environment, provided that he receives rational treatment in hospital. He does not cause a recurrence in his fellow patients, nor does he provoke secondary cases among the staff: and the infection of persons on his return home is extremely rare.

But there are many persons, particularly in the patient's environment, who have other diseases (angina, otitis, sinusitis, impetigo, etc.) also caused by hemolytic streptococci, or persons who may be healthy but are dangerous carriers of streptococci. These persons may spread streptococcal diseases, one of which is scarlet fever. It is they who, as has been said above, are to a large extent the cause of recrudescence in patients after their return home.

The *sanitization of the environment* is therefore a very important measure, which it has now become possible to accomplish thanks to penicillin. A case of scarlatina should be an incentive to the physician to undertake such measures. He should be able to work in stages and first treat persons with suspected clinical symptoms (clinical sanitization), in more serious situations undertake bacteriological examination and also treat streptococcal carriers (clinical-bacteriologic sanitization), and finally treat all contacts (general

sanitization). During our last epidemic HEDLUND and LUNDSTRÖM (1950) demonstrated that good results could be obtained by the latter method in sanitization of school classes by peroral treatment (200,000 IU × 2 in tablet form), and HEDLUND (1951) that an endemic within an institution could also be controlled on these lines.

Summary

The hemolytic streptococci are extremely sensitive to penicillin, as a rule requiring a concentration of only 0.03 IU per millilitre serum. It is possible to obtain a rapid effect in respect to sanitization of the nose and throat by administration of penicillin by injection or perorally. Recurrences in hospitals, as also secondary cases among staffs, have thereby been practically eliminated.

The streptococci reappeared, however, in an extensive number of cases a week after the return home, to the extent of 6.4 per cent of patients treated by injection and 14.2 per cent of those treated perorally. The so-called return cases have nevertheless been rare. Their number has been reduced by penicillin therapy to between one-twentieth and one-fortieth of the earlier frequency, or about 1 to 2 per mille. Peroral therapy has proved almost as effective as injection treatment for the prevention of return cases in spite of a far greater frequency in the recurrence of streptococci.

Sanitization of the environment from which the scarlatina patient comes is of great importance in combating diseases caused by hemolytic streptococci, as also for the prevention of recrudescence after the return home. Such sanitization measures should be adopted following every case of scarlatina, but should be carried out in stages.

La pénicilline comme préventif de la scarlatine.

Le streptocoque hémolytique est extrèmement sensible à la pénicilline avec une sensibilité en règle correspondant à un minimum de 0,03 UI par cc de sérum. Il est possible d'obtenir rapidement la stérilisation du nez et de la gorge par la pénicilline per os ou en injections. Les récidives et aussi la diffusion de l'infection dans les services a ainsi pu être supprimée. La réapparition des streptocoques se produit néanmoins dans un nombre important de cas dans la semaine qui suit le retour du malade à la maison dans 6,4 % des malades traités par injections et 14,2 % de ceux qui le firent par la bouche. Ces cas «de retour» ont cependant été rares. Leur nombre a été réduit par l'usage de la pénicilline à un pourcentage compris entre un vingtième et un quarantième de la fréquence antérieure, c'est à dire 1 à 2 pour mille. La thérapeutique orale s'est montrée plus active que celle par injections si l'on considère la prévention des rechutes malgré la plus grande fréquence avec laquelle on retrouve le streptocoque. La stérilisation des sujets contacts est très importante pour combattre la maladie due au streptocoque hémolytique, et aussi pour prévenir une rechute après le retour à la maison. Ces mesures sanitaires doivent être adoptées après chaque cas de scarlatine mais devraient être diffusées largement.

Penicillin zur Verhinderung von Scharlach.

Die hämolytischen Streptokokken sind außerordentlich empfindlich gegen Penicillin, in der Regel reicht eine Konzentration von nur 0,03 IE pro Millimeter Serum aus. Durch Injektion oder perorale Gabe von Penicillin ist es möglich, einen raschen

Effekt im Hinblick auf eine Sanierung von Nase und Rachen zu bekommen. Rezidive in den Krankenhäusern, aber auch sekundäre Fälle im Personalstab wurden dadurch praktisch ausgeschaltet. Dagegen treten die Streptokokken in einer wesentlichen Zahl von Fällen eine Woche nach der Heimkehr wieder auf, und zwar in einer Anzahl von 6,4 % bei Patienten mit Injektionsbehandlung und 14,2 % bei Patienten, welche peroral behandelt wurden. Die sogenannten „Heimkehrfälle" waren dessen ungeachtet selten. Ihre Häufigkeit wurde durch die Penicillintherapie auf ein Zwanzigstel bis ein Vierzigstel der früheren Frequenz, oder auf 1 bis 2 ‰ reduziert. Abgesehen davon, daß in einem größeren Prozentsatz Streptokokken wieder auftreten, hat sich die perorale Therapie als ebenso wirkungsvoll erwiesen wie die Injektionsbehandlung. Sanierung der Umgebung, aus welcher der Scharlachpatient kommt, ist von großer Bedeutung für die Bekämpfung der durch hämolytische Streptokokken hervorgerufenen Krankheiten, als auch für die Verhinderung von Wiedererkrankungen nach der Heimkehr. Solche Sanierungsmaßnahmen sollten nach jeder Scharlacherkrankung vorgenommen, aber stufenweise durchgeführt werden.

La penicilina en la prevención de la escarlatina.

Los estreptococos hemolíticos son extremamente sensibles a la penicilina, requiriendo como regla una concentración de solo 0,03 UI por mililitro de suero. Es posible obtener un efecto rápido respecto al saneamiento de la nariz y de la garganta administrando penicilina por vía oral o por inyección. De este modo han sido prácticamente eliminadas las reapariciones en hospitales así como también casos secundarios entre el personal. Los estreptococos, empero, reaparecen en un número extenso de casos una semana después de la vuelta al hogar en un 6,4 por ciento de los pacientes tratados por inyección y en un 14,2 de los tratados por vía oral. Los llamados casos «de vuelta» han sido raros a pesar de ésto. Su número ha sido reducido por la penicilina entre un 20 y un 40 de la frecuencia anterior, o aproximadamente de 1 a 2 por mil. La terapéutica por vía oral ha probado ser casi tan efectiva como el tratamiento por inyección para la prevención de los casos de vuelta a pesar de la mayor frecuencia en la reaparición de los estreptococos. El saneamiento del ambiente de donde proviene el enfermo de escarlatina es de gran importancia en las enfermedades causadas por el estreptococo hemolítico, así como también para la prevención de la recrudescencia después de la vuelta al hogar. Estas medidas de saneamiento tendrían que adoptarse siguiendo cada caso de escarlatina, pero tendría que llevarse a cabo en períodos.

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Indwelling Polyethylene Tube in the Feeding of Premature Infants

by JYRKI KAUHTIO

In July 1951, ROYCE, TEPPER, WATSON and DAY published material dealing with 30 cases of premature infants treated at the Columbia-Presbyterian Medical Center Children's Hospital, New York City, where feeding had been performed by means of an indwelling polyethylene nasal catheter. In 1952, WAGNER, JONES, KOCH and SMITH from the Cincinnati General Hospital also presented material covering 30 cases, and KUNTZ has proposed an obvious technical improvement in this method. As no papers on this subject have appeared from the other hospitals of Northern Europe, it has been considered proper to present our experience with this method. Polyethylene tube feeding was started in the premature ward of the Children's Clinic in February, 1952, and in the course of a little more than six months, 73 prematures were fed by this system.

Method

When feeding, a polyethylene tube was used, the inner diameter of which was 0.5 mm and the wall thickness 0.25 mm (Allen & Hanburys Ltd., London); it was sterilized before use by immersing it for at least 18 hours in a 1:1000 solution of Germidin "V" (A.S. Bionova, Copenhagen). Before sterilization, the sharp edges of the end of the tube were rounded off with a nail file or sandpaper, in order to avoid mucosal lesions with the tube.

In general the premature infants were deprived of food for 24 to 48 hours and in special cases even longer. The catheter was then introduced through a nostril and pushed down until it reached the stomach. The correct position of the tube was checked by injecting through the tube a small amount of sterile physiological saline solution. In no case did the tube get into the respiratory tract. The length of the tube to be inserted was determined by measuring the distance between the glabella and the point of the processus xiphoideus. The protruding end was generally about 20 cm long and was strapped to the cheek and forehead of the infant by means of plastic adhesive tape ("Sleek", Herts Pharmaceuticals Ltd., Welwyn Garden City). Into the

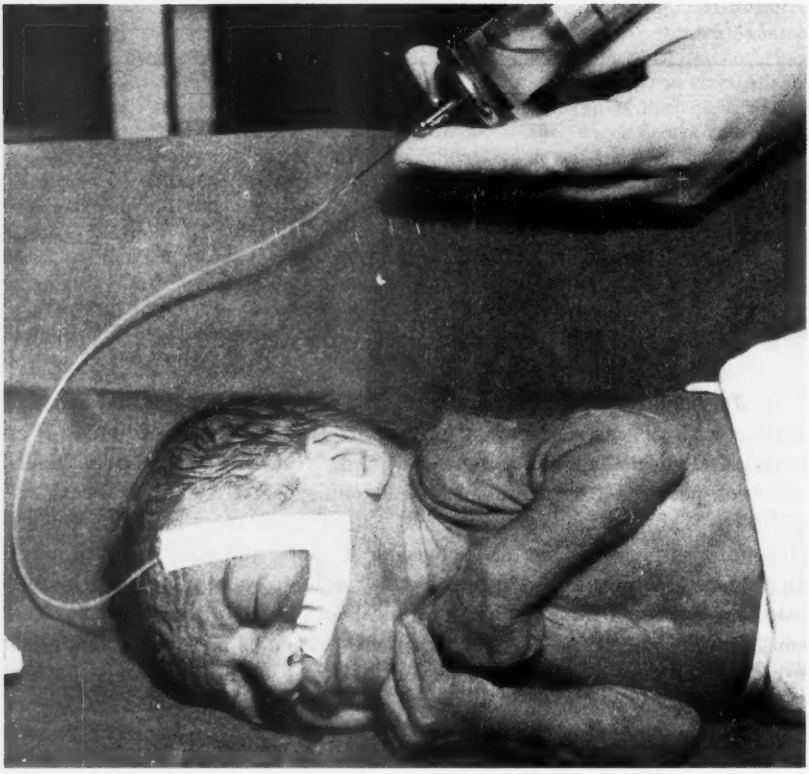

Fig. 1. Indwelling polyethylene tube in feeding premature infants.

free end of the tube, a No. 2 needle was inserted which was plugged with a metal stopper, removable when feeding.

The free end of the tube may split in the course of use, in which case the damaged part is cut off, the tube thus becoming somewhat shorter. When needed, the entire tube has been replaced, this being done in any case once a week. In some cases, the insertion of a new tube has been necessary even earlier, as an infant may get hold of the tube with its hands and pull it out.

In most cases, feeding was begun 36 hours after birth. During the first 24 hours of feeding, only a 5 % sucrose solution was injected, 1 to 5 ml at a time, 10 to 12 times a day (Fig. 1). Next day small amounts of breast milk—depending on the weight of the infant—were added and the quantity then increased gradually. After feeding, the tube was flushed with a small amount of glucose and stoppered. In no case did the tube become blocked.

Feeding was entirely or partly effected through the tube until the infant was able to take its food from a bottle.

Material

The distribution of the 73 prematures, according to birth weight, is indicated below; the figure in brackets is the number of deaths in the respective groups.

Birth weight	< 1000 g	< 1250 g	< 1500 g	< 1750 g	< 2000 g	> 2000 g
Number of cases	3 (3)	3 (2)	13 (2)	26 (1)	24	4

The boys numbered 29 and the girls 44. The age of the patients at admission varied considerably as is usual with the intake of our premature ward.

Age at admission (hours)	3	6	12	24	48	> 48
Number of cases	23	9	10	14	11	6

Usually the oldest ones had been fed already with sucrose solution during transport, and in these cases feeding was generally continued immediately after admission.

Results

Eight patients died, i.e. approximately 11 %. In 1951, 16 % of the patients of the premature ward died at an age of 48 hours or more. Of course, the two groups of patients are not strictly comparable.

In all cases of death an autopsy was performed. Intraventricular cerebral hemorrhage was found in three cases, of which one also exhibited widespread pneumonia. In one case, microcephalus plus hydrocephalus was found, whilst in four cases only immaturity was noticed, without more specific findings. In no case was there any sign of the tube having contributed to the death of the patient. In one case an oesophagitis was found, but this is not an unusual finding in newborn infants and prematures who die during the first days of life, even when not catheter-fed (AHVENAINEN).

All other cases did well. The lowest weight was reached, on an average, at the age of 6 days, and the birth weight regained towards the end of the third week of life. Premature infants are generally kept in our hospital until they reach a weight of 3 kg. In the present material, the average duration of treatment was 58 days.

Altogether, we have had experience of approximately 1,200 days of catheter feeding. The tube has usually been in use for 2 to 4 weeks, and on an average for 17 days. After this, the infants have been strong enough to take all their food from a feeding bottle. In three cases the tube was used for more than 6 weeks.

No signs of the tube disturbing the infant in any way have been noted. In five cases, before the insertion of the tube, a marked dyspnoea was present, presumed to be caused by hyaline membranes (AHVENAINEN). In no case

was the dyspnoea aggravated, and the patients recovered. The tube does not seem to affect sucking, and unless the infant is handled it usually sleeps throughout the feeding process.

No signs of local irritation caused by the tube have been noted. On only a few occasions was the part which had been in the stomach found to be covered with a layer of mucus. In one case, a transitory discharge from the nostril was observed. Sometimes, a mild irritation of the skin has been noted in the area covered by the adhesive tape, but usually only in those cases where the tube was changed more frequently than usual. In swab cultures from the nose, pharynx and skin, pathogenic bacteria have been found only rarely, while the flora did not differ in any way from that found earlier in prematures treated without the nasal catheter. Only one of the infants had thrush in the mouth.

The method has not completely fulfilled our expectations from the point of view of stopping vomiting during the first days of life. Nevertheless, in 38 patients vomiting was insignificant, whilst only 12 patients suffered from very frequent vomiting; of these, four died. One of the first cases amongst those admitted was a patient who vomited incessantly the first three weeks of life, but stopped immediately after the insertion of the catheter. We have been able to make similar observations amongst patients subject to vomiting, treated in other infant wards.

Conclusions

The use of a polyethylene nasal catheter for feeding quite obviously saves the premature infant from stress. There is less handling of the infant, which may be of importance, especially if the patient is small and in poor condition.

In the usual gavage method, a rubber tube, several times thicker than the polyethylene tube used by us, has to be introduced several times a day into the stomach. With this method, there is, in addition to the repeated stress and irritation of the mucosa, considerable risk of aspiration. The nasal catheter, however, once properly inserted, can be used for feeding for several days and only rarely need be changed.

The method saves nursing time, which is of considerable importance during the prevailing shortage of nursing staff.

The number of feedings can easily be varied as required. As the tube does not seem to disturb the ability to suck, both feeding methods may be varied at will during the transition period.

Summary

Seventy-three premature infants have been fed during the first weeks of life through an indwelling nasal polyethylene tube. Eight of them died; the cause of death being cerebral hemorrhage in three cases, congenital malformation of the brain in one case, and immaturity in four cases. The survivors did well and the average hospitalization time was 58 days. The tube was left in for an average period of 17 days, the longest time being 48 days. No complications were encountered. The method is considered to present obvious advantages as compared with the ordinary gavage method and is recommended for use particularly in the treatment of prematures who are very small or in poor condition.

Alimentation des prématurés à l'aide d'un tube de polyéthylène à demeure.

73 enfants ont été nourris pendant les premières semaines de la vie par l'intermédiaire d'un tube de polyéthylène introduit par le nez. 8 moururent à la suite des affections suivantes: 3 hémorrhagies cérébrales, 1 malformation congénitale cérébrale et 4 immaturités. Les survivants se portèrent bien et leur temps d'hospitalisation moyen fut de 58 jours. Le tube fut laissé en place pendant une durée moyenne de 17 jours avec un maximum de 40 jours. Nous ne rencontrèrent aucune complication. Cette méthode présente des avantages certains par rapport à l'ancienne technique de gavage et est particulièrement recommandée lorsqu'il s'agit de prématurés de très faible poids ou qui se trouvent dans des conditions précaires.

Polyäthylen-Dauersonde in der Frühgeborenenernährung.

73 frühgeborene Säuglinge sind während der ersten Lebenswochen durch eine in die Nase eingelegte Polyäthylen-Dauersonde ernährt worden. 8 davon starben; die Todesursachen waren in 3 Fällen cerebrale Hämorrhagien, angeborene Dysplasie des Gehirnes in einem Fall, und Unreife in 4 Fällen. Die Überlebenden gediehen gut und der durchschnittliche Krankenhausaufenthalt betrug 58 Tage. Die Sonde blieb durchschnittlich 17 Tage, längstens 48 Tage liegen. Komplikationen wurden nicht beobachtet. Es wird hervorgehoben, daß diese Methode einen wesentlichen Fortschritt im Vergleich zu den gewöhnlichen Ernährungsmethoden darstellt und daß sie vor allem für schwache oder in schlechtem Allgemeinzustand befindliche Frühgeborene geeignet ist.

Tubo de polietileno de permanencia continua en la alimentación de niños prematuros.

73 niños prematuros fueron alimentados durante las primeras semanas de la vida a través de un tubo nasal de polietileno de permanencia continua. Ocho de ellos murieron habiendo sido la causa de muerte hemorrágica cerebral en tres casos, malformación del cerebro congénita en uno e immaturidad en cuatro casos. Los supervivientes continuaron bien y el tiempo medio de hospitalización fué de 58 días. El tiempo medio en que el tubo permaneció en nel niño fué de 17 días, la permanencia más larga de 48 dias. No se presentaron complicaciones. Se considera que el método tiene grandes ventajas comparado con el método de alimentación forzada ordinario y se recomienda su uso particularmente en el tratamiento de los prematuros que son muy pequeños o estan en malas condiciones.

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The Response of Idiopathic Renal Acidosis to Oral Sodium Lactate

by THOMAS STAPLETON

Attention was first drawn by LIGHTWOOD (1935) to the disorder of infancy now known in this country as idiopathic or primary renal acidosis. The syndrome has been described by BUTLER, WILSON and FARBER (1936), HARTMANN (1939), PETERMAN (1945), PAYNE (1948), BOURTOURLINE-YOUNG (1949), STAPLETON (1949), POWELL (1949), COOKE and KLEEMAN (1950), KELSEY, REINHART and FISHEL (1950), LATNER and BURNARD (1950), ENGEL (1951), HUTCHISON and MACDONALD (1951), and DOXIADIS (1952).

It has been shown that prolonged treatment with alkalis such as sodium lactate or sodium citrate usually leads to recovery. It was not known what effect this treatment had on the excretion of electrolytes. The present study records the effect of treatment on the electrolyte-balance of sodium, potassium and chloride.

Methods

Blood samples were either venous ones obtained from the jugular vein, or capillary ones from a heel prick collected into Hinton tubes as described by DAVIES. Sodium and potassium were estimated by flame photometry; chloride by iodometric titration (VAN SLYKE and HILLER); total carbon dioxide content of serum using Van Slyke's manometric apparatus; calcium by the method of Kramer and Tisdall (HARRISON); phosphorus by KING; blood urea by Archer and Robb (HARRISON). During the balance studies the child was kept on a metabolic bed of the type described by HOAG. The amount of milk taken was estimated by weighing the bottles at the beginning and end of each period. Each day's milk was analysed. Specimens of milk and stool were prepared for analysis by making nitric acid filtrates as described by WALLACE *et al.*

Case History

The patient, a male infant, the seventh child of healthy parents, was born by normal delivery at term. The next sibling was twelve years old. The mother was aged 42 years and was well throughout pregnancy. The baby's birth weight was 7 lbs. 9 ozs. (3,322 g). He was breast fed for ten weeks. The mother then had a mild illness diagnosed as "'flu" and the baby's feed was changed to Ostermilk No. 1. He continued

to thrive and at the age of twelve weeks weighed 12 lbs. 7 ozs. (5,639 g). The feeds were then changed to Ostermilk No. 2. From that time he became difficult over his feeds, would not take the whole feed and often vomited a portion. He became relatively constipated; while being breast fed he had usually passed four motions a day; now he would only pass one every other day. The mother stated that she had noticed no change in the volume of urine passed. At the age of 14 weeks the feeds were changed back to Ostermilk No. 1 and still he would not take his whole feed, although he ceased to vomit.

He had been given the normal amounts of orange juice and cod liver oil. (He was started on 2–3 drops daily of Cod Liver Oil Compound (U.K. Ministry of Food) at the age of four weeks and this was gradually increased to two teaspoonfuls (i.e. 1400 IU) daily at the age of eight weeks.) At the age of 17 weeks he was seen by Dr. F. S. W. BRIMBLECOMBE at Paddington Green Children's Hospital: His weight then was 13 lbs. 2 ozs. (5,957 g); although small, he was not dehydrated. Advice about management was given. Two weeks later his weight had fallen to 12 lbs. $13^1/_2$ ozs. (5,823 g). Dr. BRIMBLECOMBE believed that he might be suffering from renal acidosis and arranged for his admission to the children's ward of St. Mary's Hospital on 22nd January, 1952.

When admitted there he seemed to be a lively baby taking an interest in his surroundings. There was no clinical dehydration and no fever. He was small for his age and this seemed to be the result of failure to grow rather than of a wasting disease. His muscle tone was normal. Systematic examination revealed no abnormality in the pulmonary, cardiovascular or nervous systems. No faecal masses were felt in the abdomen. The urine was acid to litmus paper, contained a trace of albumin and pus cells were seen in the deposit. There was a scanty growth of Streptococci faecalis. Examination of the jugular venous blood showed a low total carbon dioxide content (9.8 mEq/l) and a raised serum chloride (124.5 mEq/l).

The day after admission a further examination of the urine showed it to be neutral and to contain a very few pus cells. The blood urea was raised (63 mg per 100 ml) and the serum calcium was raised (15 mg per 100 ml). A diagnosis of idiopathic renal acidosis with hypercalcaemia was made. The results of subsequent chemical examinations are shown in the Table and are discussed below.

Treatment and Progress

During the week following admission his weight fell to 12 lbs. $10^1/_2$ ozs. (5,741 g) and he became clinically slightly dehydrated. His stools were small and hard.

Treatment with sodium lactate was begun a week after admission, that is at 19 weeks of age. The medicine was given mixed with his feeds. The amounts given are shown in the Table. The initial dose (90 mEq sodium, which is the equivalent of 10 g sodium lactate) was too high and produced watery stools. Adjustment of the dose relieved this. Following the start of treatment his weight increased rapidly for a few days, but not all of this initial gain was maintained.

When 23 weeks old he developed a respiratory infection. He was given a seven-day course of chloromycetin. During this infection his liver became larger and was palpable three finger-breadths below the costal margin. Further specimens of urine showed occasional pus cells on microscopy. Cultures were sterile.

Throughout his stay in hospital he was very difficult to feed and required much coaxing. Attempts to introduce thickened feeds or solids were unsuccessful. On several

TABLE 1

Age in weeks	Day of balance study	Oral sodium lactate as mEq Na/day	mEq/l				mg per 100 ml		
			Serum Na	Serum K	Serum Cl	Serum CO_2	Serum Ca	Serum P	Blood Urea
18	First study		147	4.7	124.5	9.8			
	1						15.0	5.2	63
	2		159	5.5	125.2				72
	3		159	5.1					
	6		164	5.7	134.0				
19	7	90		5.0	133.0		12.2	5.1	69
			168		136.2	16.3			
	8	90	180	4.5	134.5				
	9	90			116.7				
	10	45		4.6	131.0				
	11				129.7				
	12	45			129.0				
20	14	45	168		120.4	24.8			
	16	60			127.6				
	19	60	169	5.6	118.4				
						29.0	10.6		45
27		200			123.0	19.7	15.0	5.7	55
31		200	170		135.5	18.0	12.0	6.2	58
	Second study								
34	2	200	161	4.8	116.5				
35	5		155		112.5	26.8			
	6		147	5.5	116.9		11.4	6.0	52
	7		150		120.8				
	8				114.4				
36	end		147		113.2	14.9	13.2		46
39		50			114.5		12.8	5.7	37
43			138	5.2	108.0	22.2	12.0		35
56			145	4.3	105.7	21.3	12.0	5.5	40
73			145	5.1	105.5	17.7	10.9		31

occasions his temperature rose to 102° F for 12 to 48 hours and this pyrexia could not be correlated with dehydration or with any infection.

Gradually he improved and left hospital at the age of 26 weeks, weighing 13 lbs. 14 ozs. (6,297 g). At home he was fed on cow's milk and was given sodium lactate containing 200 mEq sodium a day. His mother was advised not to give him any vitamin D supplement because of the high level of serum calcium. During the next few weeks his mother persuaded him to take Farex, Marmite and strained meat and vegetable foods. He continued to have occasional spikes of fever. His weight rose to 14 lbs. 14 ozs. (6,737 g) and his improvement was maintained.

At the age of 34 weeks he was admitted to hospital for 2 weeks in order that his response might be studied when the administration of sodium lactate was stopped.

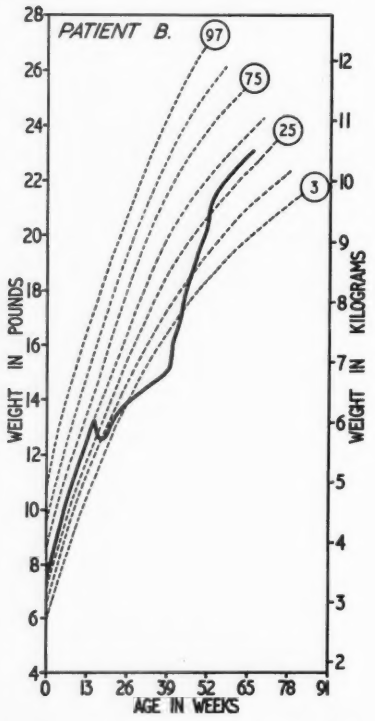

Fig. 1. The weight shown superimposed on a percentile chart of normal growth. (The percentiles are taken from the data of H. C. STUART.)

The sodium lactate was abruptly stopped. During the subsequent four days he lost 11 ozs. (321 g), became rather miserable and started to vomit. The administration of sodium lactate in a dose providing 80 mEq sodium a day caused an immediate improvement in his clinical condition. At 38 weeks of age he weighed 16 lbs. 6 ozs. (7,428 g) and the dose of lactate was further reduced to provide 50 mEq sodium a day. The sodium lactate was finally stopped at the age of 39 weeks. His progress was maintained. He had no further spikes of fever after his second admission. By the age of 43 weeks his blood urea was normal.

At the age of 56 weeks his development appeared to be normal for his age; he weighed 21 lbs. $5^1/_2$ ozs. (9,686 g), was firm and well-nourished. His appetite was fairly good although he remained reluctant to take any solids which required chewing. The only abnormality, clinical or chemical, found was a raised serum calcium (12.0 mg per 100 ml).

At the age of 73 weeks he seemed normal in every way. He weighed 23 lbs. 8 ozs. (10,660 g). The serum calcium was normal.

During the period when he was ill, his weight fell below the 3rd percentile. He had returned to his normal channel of development by the end of treatment. (Fig. 1.)

Other investigations:

Haematological: The erythrocyte count and haemoglobin respectively were 3.3 million per cmm and 10.4 g per 100 ml at 20 weeks, 3.6 and 10.4 at 23 weeks, 4.0 and 11.2 at 27 weeks, and 4.3 and 11.9 at 35 weeks of age.

The sedimentation rate was 14 mm in one hour (Westergren) at 19 weeks.

The fasting blood sugar was 80 mg per 100 ml at 23 weeks.

A pyelogram following the subcutaneous injection of dye with hyaluronidase did not outline the kidneys satisfactorily, but was regarded as probably normal.

X-rays of the chest, abdomen and bones both early in the disease and after recovery showed no abnormalities.

Urine. A two-way paper chromatogram at the age of 35 weeks showed a normal concentration of amino-acids and a normal "T" pattern.

Electrocardiographs at the age of 19 and 20 weeks showed no unusual pattern.

The biochemical findings and electrolyte-balance studies

Studies of the electrolyte-balance were made at two stages of the disease, (1) shortly after his first admission to hospital at the age of 18 weeks and (2) at the age of 34 weeks after he had been treated for fifteen weeks.

During the first study (six days immediately before treatment was commenced and for the following twelve days), the effects on the electrolyte-balance of initiating treatment with sodium lactate were observed. During the second study he was observed on treatment for four days, the administration of sodium lactate was then stopped, and measurements were continued for a further four days, thus giving the picture of the electrolyte-balance following an abrupt cessation of treatment.

The biochemical findings in the blood were notable for the following features (Table and Fig. 2).

The initial serum sodium value was within normal limits.

When the first electrolyte-balance study was begun, the serum sodium had risen to 159 mEq/l and after the first day of treatment with sodium lactate was 168 mEq/l. The serum chloride, which was high (124.5 mEq/l) when the infant was first seen, had risen to 136 mEq/l and the total carbon dioxide content to 16 mEq/l. Thus, there was a state of hyperelectrolytaemia (RAPOPORT). The serum sodium and the serum chloride both remained high from the 18th to the 35th week of age. The serum chloride tended to be high until the acidosis finally disappeared. One must distinguish between the rise in the chloride value associated with the general hyperelectrolytaemia and the rise in sympathy with the low bicarbonate values.

The total carbon dioxide content of the serum was very low when the infant was first seen (9.8 mEq/l) but rose to 16.3 mEq/l soon after treatment was started. During the second study of the electrolyte-balance it became evident that treatment could not yet be discontinued because on stopping

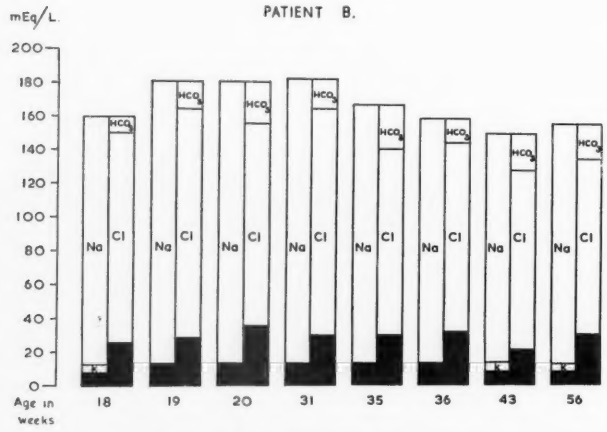

Fig. 2. The electrolyte-pattern of the serum.

the administration of sodium lactate, the total carbon dioxide content of the serum fell from 26.8 mEq/l to 14.9 mEq/l. The last two determinations at the ages of 43 and 56 weeks, made after treatment had been stopped for some time, were 22.2 and 21.3 mEq/l.

The level of serum potassium was normal throughout. The blood urea, which was raised during the early stages of the disease, fell to normal by the age of 39 weeks.

The serum calcium was raised at the time of nearly all examinations. It was once normal at the age of 21 weeks. It was still raised when the child was 56 weeks old, but was normal by 73 weeks.

The serum inorganic phosphorus was normal at all times.

The first study of the electrolyte-balance

This showed the effects of initiating treatment and the analysis of the results obtained can conveniently be considered in two parts; the findings during the first six days when no therapy was given and those during the next twelve days following the start of treatment (Figs. 3–6).

Control period or first six days

The daily sodium and chloride balances showed an apparent positive balance during each period of a day, although the extent of the positive balances varied. The cumulative balance showed that there was an apparent positive balance of 55 mEq/l of sodium and 47 mEq of chloride. During this

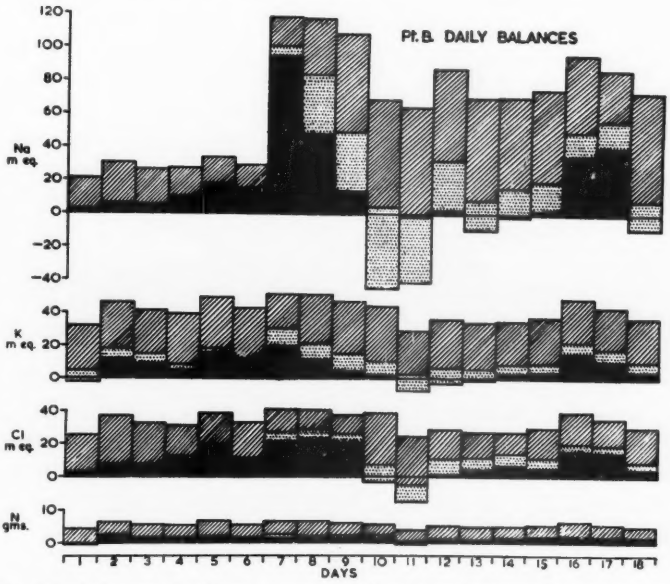

Fig. 3. The daily balances of sodium, potassium, chloride and nitrogen during the first study of the electrolyte-balance. The height of the column above the base line represents the intake, the hatched area the output in the urine, the dotted area the output in the stools and the black area a positive balance. Negative balances are shown below the base line.

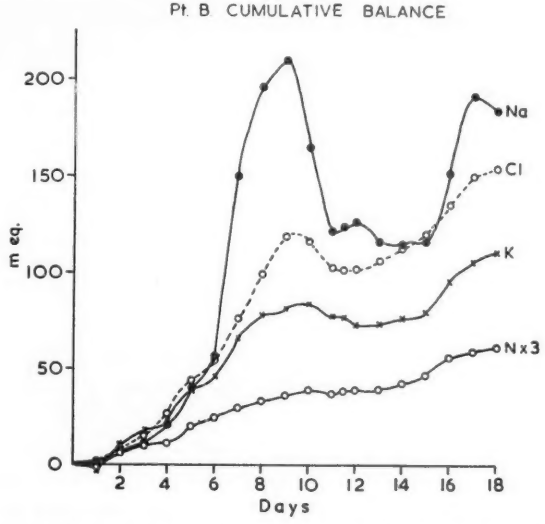

Fig. 4. The cumulative balances during the first study. The nitrogen is expressed in g x 3.

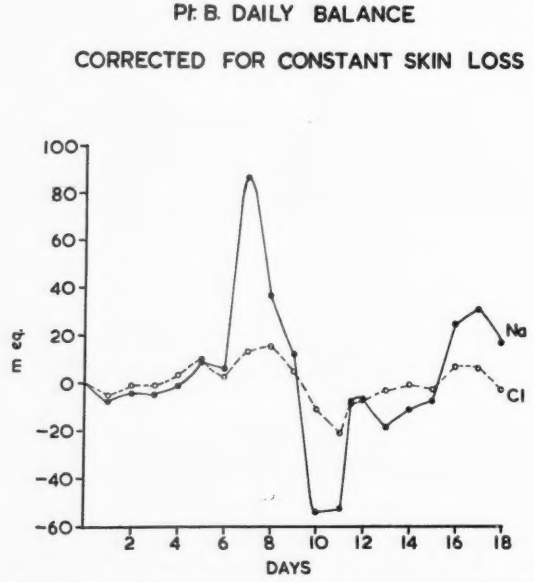

Fig. 5. The daily balances corrected for a theoretical and constant loss of sodium and chloride through the skin. The apparent positive balance found during the control period has been taken to represent the loss through the skin.

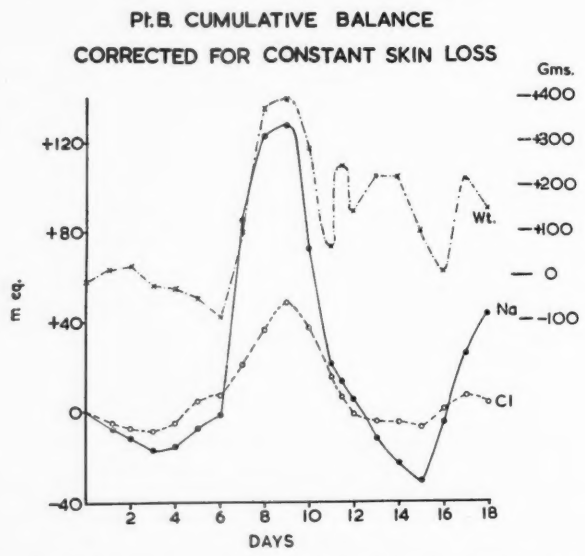

Fig. 6. The cumulative balances corrected for a theoretical and constant loss of sodium and chloride through the skin. The actual daily changes of weight (in g) referred to his weight at the time of starting the first study.

time the infant lost 85 g in weight. Previous observations on normal children (GAMBLE, STAPLETON) have shown that there is normally a large loss of sodium and chloride through the skin. It is reasonable to suppose that the major part, if not all, of these apparent positive balances was really accounted for by losses through the skin.

The potassium and nitrogen balances were both positive and the potassium balance (expressed in mEq) exceeded the nitrogen balance (expressed in g × 3) by a considerable amount. This finding was unexpected and the explanation of it is not apparent. Whether it implied an undue retention of potassium, or an excessive loss through the skin, cannot be decided.

The effect of giving sodium lactate

The therapeutically desirable amount of sodium lactate to be given each day had to be determined by trial and error. During the first three days there was a marked retention of sodium accompanied by a rapid rise in weight. By the fourth day the renal excretion of sodium had increased to such an extent that, together with the looseness of the bowels, it fully compensated for the large daily sodium intake. By the end of the fifth day of treatment, the excess sodium load was being excreted and subsequently the renal excretion remained high. The rather large positive balance of sodium found on the 16th and 17th days of the study may have been caused by spontaneous variations in renal excretion accentuated by the slightly increased oral intake on those days.

If one makes the assumption that the apparent positive balances of sodium and chloride during the control period represented the loss through the skin and that this loss remained approximately constant throughout the eighteen days of the study, one can make a correction to the balance so as to obtain a picture of the actual retentions. The effect of making this calculation for the insensible loss of sodium and chloride on the daily balances is shown in Fig. 5 and on the cumulative balance in Fig. 6. One sees that there was a complete adjustment in six days to the altered intake (i.e. the load presented for excretion). The reasonableness of this correction is shown by the very small variation which occurred in the chloride balance, although in the corrected cumulative balance there was a moderate retention of chloride for three days after the start of treatment.

The weight changes followed the sodium balances fairly closely.

The potassium and nitrogen balances were little influenced by the change in sodium intake. The only change was that the rather excessive positive potassium balance during the control period (that is, excessive when compared with the nitrogen balance) became practically parallel to the nitrogen balance when they were represented on comparable scales.

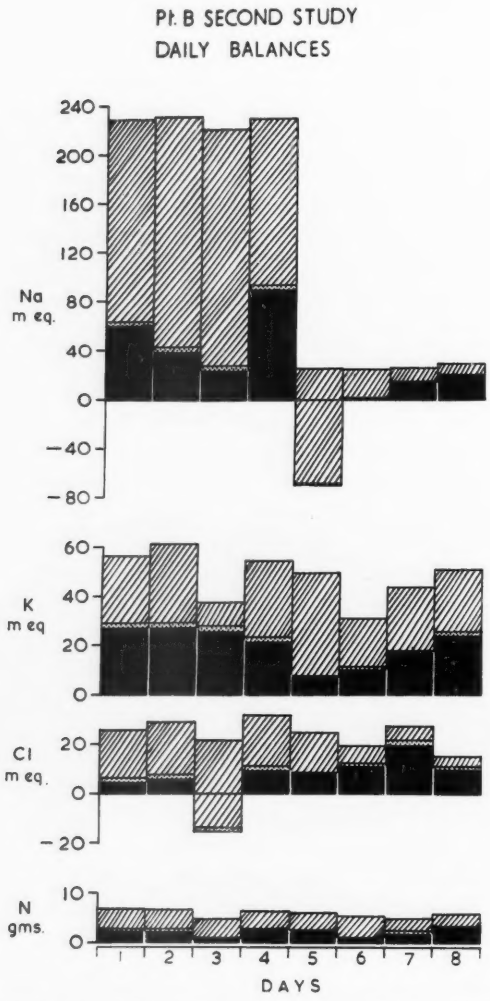

Fig. 7. The daily balances during the second study of the electrolyte-balance.

The effect on the electrolyte-balance of stopping the administration of sodium lactate

The patient was readmitted to hospital at the age of 35 weeks, so that the effect of abruptly stopping the treatment could be observed (Figs. 7 and 8). He had been on a constant daily dose of sodium lactate containing 200 mEq sodium. Usually in managing this type of case one gradually decreases the

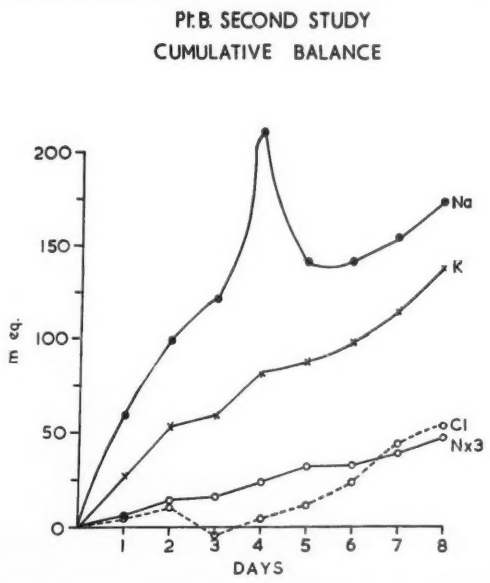

Fig. 8. The cumulative balances during the second study.

dose of alkali, but it was felt that a clearer picture of the effect on the excretion of electrolytes would be obtained if the treatment were stopped abruptly. Measurements were made for 4 days while he continued to receive the same dose of sodium lactate, the lactate was then stopped and measurements continued for a further four days. That these observations were made at a time when he had not fully recovered from his disease, was shown by the chemical changes in the blood. The total carbon dioxide content of the serum fell from 26.8 to 14.9 mEq/l. Curiously this was not associated with a rise in the serum chloride above its very high level, but with a fall in the serum sodium.

The sodium balance showed a rapid diminution in the urinary sodium output; in fact the renal mechanisms for conserving sodium were so efficient that within 48 hours he showed an apparent positive sodium balance. By the end of the third day this was approximately the same as that seen during the original control period before he had any treatment.

The chloride balance was rather irregular and was negative on the third day of the study.

The potassium balance was positive throughout, but during the first three days after the cessation of treatment to a smaller degree.

Discussion

The exact disturbance of the normal physiology which underlies renal acidosis in infancy is not known. This patient does not present the simple and uncomplicated picture of idiopathic renal acidosis. The chemical picture shows not only acidosis with hyperchloraemia, but also hypercalcaemia and hyperelectrolytaemia. The condition of infantile hypercalcaemia of unknown aetiology has been described by LIGHTWOOD (19, 20) who stated that some cases are associated with renal acidosis. The hyperelectrolytaemia cannot be explained on the basis of dehydration as it was present in its absence. The high levels of serum chloride were not accounted for merely by the low levels of serum bicarbonate as there was a parallel rise in the serum sodium. Clinically the infant was similar to the cases of idiopathic renal acidosis with hypercalcaemia (LIGHTWOOD, 20), and the therapeutic response followed the usual course observed in uncomplicated renal acidosis. It seems reasonable to suppose that the disorder underlying the acidosis was the same as that in other reported cases of idiopathic renal acidosis.

Various theories have been advanced to account for the acidosis. LIGHTWOOD (18) noted the frequent association with calcium deposits in the kidneys, but many cases (LIGHTWOOD, MACLAGAN and WILLIAMS, HARTMANN, STAPLETON (30), KELSEY, REINHART and FISHEL, HUTCHISON and MACDONALD) have shown no X-ray evidence of calcification. The observation that calcium deposits are often found on histological examination in the kidneys of children dying from other conditions (MACGREGOR), makes it more reasonable to suppose that calcium deposition is not the primary trouble.

HARTMANN suggested that there was a loss of bicarbonate in the urine. STAPLETON (30) considered that the loss of bicarbonate in the urine might have been due to interference with the enzyme carbonic anhydrase. This concept fitted in with the work of PITTS *et al.* (26, 27) on the reabsorption of bicarbonate by the renal tubules.

A failure of the kidneys to form ammonia was thought to be an unlikely explanation on quantitative grounds (STAPLETON, 30). LATNER and BURNARD have since shown that infants with this condition can form ammonia as well as normal infants.

The present study ascribes the renal response, in so far as that response can be assessed by a balance-study, both to an increased load of sodium and to the abrupt cessation of that load. The reservation "in so far as that response can be assessed by a balance-study" is an important one for two main reasons. First, the changes carried out by the kidney in regulating the balance of sodium and many other ions are very large in a quantitative sense, while the changes necessary to upset the acid-base situation of the body in respect

to those same ions are relatively very small. Secondly, evidence is accumulating to show that tissue composition is not as constant as was at one time supposed; it can alter not only as a result of induced deficiencies (COTLOVE *et al.*) but also following less gross changes in the electrolyte-composition of the diet (WALLACE, 35).

With the above considerations in mind, one can say that no interference with the mechanisms for excreting sodium was demonstrated. The general pattern of the electrolyte-balance following the continued administration of a load of sodium lactate was similar to that found in normal children by GAMBLE *et al.* Thus one can conclude that the overall response to a load of sodium lactate was normal, but that the method of study was not sensitive enough to reveal finer changes in the renal adjustment. Such changes may have been further obscured by the fact that the infant was given a larger load of sodium lactate than were the normal children studied by GAMBLE *et al.*

The second study clearly demonstrated that within the limits of the method of investigation there was no interference with the renal mechanisms for conserving sodium in the face of an abrupt decrease in the sodium intake.

These two observations are quite consistent with the concept that the renal defect is one concerned with the regulation of bicarbonate excretion (STAPLETON, 30). No indication is given as to the nature of the base component which must inevitably be associated with the increased excretion of bicarbonate.

The phenomenon of potassium loss following the administration of sodium was described by BUNGE, but this loss is not usually sustained. DOXIADIS has suggested that it would be preferable to treat children with renal acidosis by giving a mixture of sodium and potassium salts in the ratio of 2 : 1, as he thought that the prolonged administration of sodium salts would be likely to cause or accentuate potassium deficiency. In the present study no potassium deficiency occurred and the increased sodium lactate intake had practically no effect on the potassium balance. The urinary concentration of potassium remained remarkably constant. From this it may therefore be concluded that there is probably no advantage in giving a mixture of sodium and potassium salts, rather than sodium salts alone, out of regard for a theoretical risk of inducing a potassium deficiency.

Summary

A case of idiopathic renal acidosis with coincident hyperelectrolytaemia and hypercalcaemia is described. The renal response to the administration of sodium lactate is examined and it is shown that the overall response is similar to that which would occur in a normal child. The prolonged administration of sodium lactate did not cause a depletion of potassium. The findings are consistent with the hypothesis that

the underlying defect is a failure on the part of the kidney to regulate the excretion of bicarbonate.

The author wishes to thank Dr. R. LIGHTWOOD who was in charge of the case for his help, Dr. W. M. WALLACE for commenting on the findings, Dr. P. H. SANDERSON for advice and for assistance with the sodium and potassium determinations, Dr. V. WYNN for allowing the author to use his flame photometer, Mr. I. W. J. EVANS for technical help and Sister J. CAMPBELL for her skilful nursing care.

Les effets du lactate de soude par voie orale dans l'acidose rénale idiopathique.

L'auteur décrit un cas d'acidose rénale idiopathique avec hyperélectrolytémie et hypercalcémie. Il a étudié la réponse du rein à l'administration de lactate de soude elle est semblable à celle obtenue chez l'enfant normal. L'administration prolongée de lactate de soude ne provoque pas de fuite du potassium. Les résultats concordent avec l'hypothèse, que l'affection serait due à une incapacité du rein, à régler l'excrétion du bicarbonate.

Die Reaktion der idiopathischen, renalen Acidose auf orale Natriumlaktatzufuhr.

Es wird ein Fall von idiopathischer, renaler Acidose mit gleichzeitiger Hyperelektrolytämie und Hypercalcämie beschrieben. Die Reaktion der Niere auf die Applikation von Natriumlaktat wurde geprüft, wobei sich herausstellte, daß sie der eines normalen Kindes ähnlich ist. Die über längere Zeit sich erstreckenden Natriumlaktatgaben verursachten keine Verminderung des Kaliums. Die Resultate stimmen mit der Hypothese überein, daß der zu Grunde liegende Defekt in einem Unvermögen der Niere, die Bikarbonatexkretion zu regulieren, zu suchen ist.

Respuesta de la acidosis renal idiopática al lactato de sodio por vía oral.

Se describe un caso de acidosis renal idiopática con coincidencia de hiperelectrolitemia y de hipercalcemia. La respuesta renal a la administración del lactato de sodio es estudiada y se demuestra que esa respuesta es similar a la que ocurre en un niño normal. La prolongada administración de lactato de sodio no produjo descenso del potasio. Los hallazgos están de acuerdo con la hipótesis de que se trata de un defecto en la parte del riñón que regula la excreción del bicarbonate.

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The Influence of Phenylalanine Intake on the Chemistry and Behaviour of a Phenylketonuric Child

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There are at least three inborn errors of metabolism, galactosaemia, hepatolenticular degeneration and phenylketonuria, associated with mental or neurological changes. In galactosaemia mental development becomes more normal if galactose is removed at an early age from the diet (UNSHELM, DU SHANE and HARTMAN, and BRAY, ISAAC and WATKINS). In hepatolenticular degeneration some improvement can be obtained when treatment aimed at removing copper from the body is instituted (DENNY-BROWN and PORTER, and CUMINGS). In phenylketonuria, no treatment, so far as we are aware, has hitherto proved helpful.

Phenylketonurics, apart from mental deficiency, usually have fair hair, a musty, mouse-like smell, wide spacing of incisor teeth, some degree of microcephaly, brisk reflexes, epileptic fits and hyperkinetic movements, often with stereotyped digital mannerisms; eczema is also common. The patients are well built and have a normal expectation of life. The disorder has its onset in infancy and is determined by an autosomal recessive gene. There are probably 1600 cases in Great Britain alone (MUNRO).

The essential metabolic error in phenylketonuria is an inability to convert phenylalanine to tyrosine. Phenylalanine accumulates in the blood and cerebrospinal fluid, and is excreted in the urine either unchanged or as phenylpyruvic acid (FÖLLING), phenyllactic acid (JERVIS, BLACK, BOLLING, and KANTZE), or phenylacetic acid (WOOLF 1951). Unlike phenylalanine, phenylpyruvic and phenyllactic acid are not present in the blood in detectable amounts. The incorporation of phenylalanine into the proteins of liver, kidney, brain and plasma is undisturbed (BLOCK *et al.*).

It has been suggested that the mental retardation in this disease may be due to a secondary tyrosine deficiency. This is unlikely, for the addition of tyrosine to the diet leads to no appreciable improvement in the mental state of these subjects (MAUTNER and QUINN, COWIE, and STEINBORN). Moreover, blood levels of tyrosine have been found to be normal or only slightly

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decreased (BLOCK *et al.*, JERVIS, own observation). It therefore seemed to us that it might be the high level of phenylalanine, or of its breakdown products, which interfered with mental function. As one of us had under his care a two year-old child with phenylketonuria we decided to try to provide her with a phenylalanine-restricted diet.

The Preparation of the Diet.

This was initially free from phenylalanine. The necessary salts, vitamins, fats and carbohydrates were provided in the pure state; the only source of nitrogen was an acid casein hydrolysate (Allen and Hanburys Ltd.), treated to remove phenylalanine and tyrosine by adsorption on activated charcoal, which had been further treated with 5 per cent acetic acid (BLOCK and BOLLING). The 10 per cent hydrolysate was shaken twice, each time for one hour with fresh charcoal, and finally run through charcoal columns until the filtrate produced no growth when added to an inoculated phenylalanine-free medium. 1.5 g L-tyrosine, 0.25 g L-tryptophane and 0.7 g L-cystine per day were then added to the hydrolysate, except during the tyrosine-free period (the first five days of the experiment), when only tryptophane and cystine were added. The amount of casein hydrolysate ingested daily was equivalent to approximately 10 g protein; the diet provided about 1100 calories daily. The protein intake was limited because hydrolysed casein is expensive and its special preparation is difficult.

Later phenylalanine was added to the diet in limited quantities. As ROSE's tentative value for the minimum adult daily requirement of phenylalanine is 1.1 g, 0.6–0.8 g of phenylalanine in the form of 400–500 ml of milk was added daily to the above diet, thus providing altogether 20 to 25 g protein. When the child was sent home, the mother adhered strictly to a diet consisting mainly of vegetables, fruits and sugar, with 1 oz. oatmeal or rice, 300–400 ml of milk and 100 ml of the 10 % phenylalanine-free casein hydrolysate daily. This diet contained 20–28 g protein, 0.8–1.1 g phenylalanine, and furnished approximately 1100—1200 calories (MCCANCE and WIDDOWSON, BLOCK and BOLLING); two-thirds of the phenylalanine was provided in the milk. After some weeks it became evident that this diet provided more phenylalanine than the child needed, for she gained weight rapidly, and the phenylalanine level in the blood and phenylpyruvic excretion in the urine were still raised. The milk was therefore reduced to 200 and later to 100 ml daily and gluten-free wheat flour substituted for oatmeal or rice. To compensate for the reduced protein intake, an extra 100 ml of 10 % phenylalanine-free casein hydrolysate was given. On this modified menu, which contains the equivalent of 17 g protein and 0.3 g phenylalanine daily, the child is gaining weight satisfactorily, the phenylalanine blood level has become normal and no more phenylpyruvic acid is excreted in the urine. The daily diet-sheet is as follows:—

8 a.m.	Gluten-free wheat flour *ad lib.* in water. 100 ml of milk, sugar *ad lib.*
10.30 a.m.	100 ml of the 10% phenylalanine-free casein hydrolysate.
11.30 a.m.	Orange juice with sugar.
1.30 p.m.	6–8 oz. cabbage, turnips or swedes boiled in water. 1 oz. butter, 1–2 oz. grated apple or banana. Sugar *ad lib.*
4 p.m.	10–12 oz. grated or cooked apples with sugar. Multivitamine drops, "Protovite" brand Roche, 1 ml daily.
6 p.m.	100 ml of the 10% phenylalanine-free casein hydrolysate.

Biochemical Methods.

In the blood phenylalanine and tyrosine were determined by microbiological assay of heparinised plasma taken in the post-absorptive state. The technique was essentially that of HENDERSON and SNELL and of SCHREIER and PLÜCKTHUN, the test organism being *Lactobacillus arabinosus* for phenylalanine and *Leuconostoc mesenteroides P-60* for tyrosine. Two standard curves were added to each batch of assays, and each plasma specimen was assayed in duplicate. As the child was incontinent, she was kept on a metabolic bed and a special plastic apparatus for collecting 24-hour urine specimens was prepared according to the description of BLACK. The urine was collected under toluol, transferred every twelve hours to a refrigerator and kept at –10°C. Phenylpyruvic acid estimations were carried out within the next two days using the dinitrophenylhydrazine method of PENROSE and QUASTEL, though in this disease the method gives results which are rather too high (BERRY and WOOLF). Phenylalanine in urine was estimated by two-dimensional paper chromatography (CONSDEN, GORDON, and MARTIN, DENT 1947). At least two chromatograms of each urine specimen were prepared and the phenylalanine spots were compared with test spots of 10–20–30–40–50 and 60 µg pure phenylalanine run at the same time and under identical conditions. The margin of error of this method is believed to be less than 25 per cent, which is of little importance in view of the large quantities of phenylalanine found in the urine of patients with this disease. Other changes in the aminoacid pattern of the urine were also demonstrated by paper chromatography. Tyrosine in the urine was estimated by microbiological assay.

Case Record and Results

The child who is the subject of this paper was born in October 1949; delivery was normal at term and her birth-weight was $8^1/_4$ pounds (3.7 kg). Her two siblings and mother are mentally normal and there is no phenylalanine or phenylpyruvic acid in their urine. The father is said to be healthy, but was not available for examination. There is no consanguinity of the parents. The child had no illnesses during infancy, but her mental development was slow and she did not sit up until she was 18 months old. At the age of two she could not stand, walk or talk, she showed no interest in her food or her surroundings, and lay in her cot groaning and crying for hours at a time, frequently rolling her head from side to side and banging it on her pillow. The skull circumference was $18^1/_2$ inches (47 cm), her weight 27 pounds (12.2 kg). She had fair hair, a rough skin with some eczema of the face and a typical mouse-like smell. The tendon reflexes were exaggerated, but the muscle tone was normal, the plantar responses were flexor. The liver was not enlarged. The blood count and cerebrospinal fluid were normal, as was the electrocardiograph.

Biochemical Investigations. — On a normal diet (October 1951): plasma total cholesterol 150 mg%, free cholesterol 63 mg%, albumin 3.4 g%, globulin 2.4 g%, non protein nitrogen 22 mg%, Takata 000001, thymol turbidity 1 unit. Plasma and urine chromatograms showed a striking increase in phenylalanine, otherwise the aminoacid pattern was normal. Phenylalanine content of plasma 67 mg% (normal av. 1.6 mg%[1]), of urine about 500 mg/24 hrs. (normal up to 8 mg/24 hrs.[1]). Tyrosine content of plasma 0.92 mg% (normal av. 1.6 mg%[1]). $FeCl_3$-test in urine olive-green, phenylpyruvic acid quantitative

[1] SCHREIER and PLÜCKTHUN and SCHREIER personal communication.

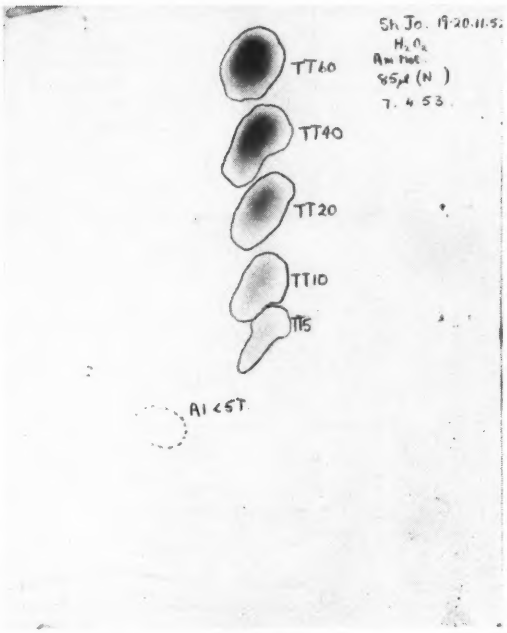

Fig. 1 a.

Fig. 1. Urine chromatograms of the patient a) November 1952 on a phenylalanine-restricted diet, b) 12 days later on 4 g L-phenylalanine daily. The urine volume used was 1/10,000 of the 24 hr.-volume. The chromatograms were treated with perhydrol and ammonium molybdate. TT = test taurine spots from 5, 10, 20, 40 and 60 μg taurine. Al, alanine; Cy, cysteic acid; Glu, glutamine; Gl.a., glutamic acid; Gly, glycine; Hi, histidine; Ly, lysine; Ph, phenylalanine; Se, serine. Figures beside aminoacid names indicate colour intensity of spots as compared with taurine test spots (e.g. 10 T = colour equal to 10 μg taurine). Note the great increase of phenylalanine in b). The other aminoacids seen in b) are also slightly increased if compared with a), but they are still within the normal range.

364 mg/24 hrs. Urine contained no protein, no sugar, and no cellular elements. There was no urobilinogenuria in fasting urine specimens.

In December 1951 this child was put on to a phenylalanine-free diet for six weeks. There was no immediate or dramatic change in her mental state, but the phenylalanine content of the plasma and urine gradually fell to normal levels (Figs. 1a and 2) and the excretion of phenylpyruvic acid dropped to 38 mg/24 hrs. The $FeCl_3$-test became negative. The tyrosine content of the plasma during the first five days of tyrosine-free food dropped to such low levels that it was no longer measurable, although the phenylalanine level in plasma was at this time still high. She rapidly lost weight, so tyrosine (1.5 g daily) was added to the diet. The tyrosine level in the blood then rose to

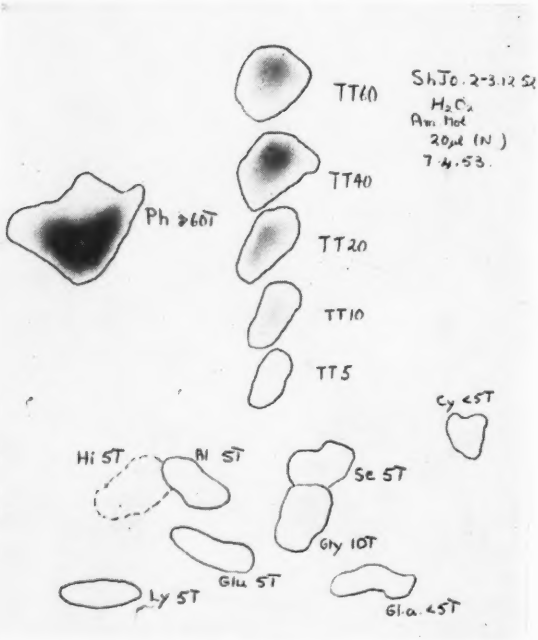

Fig. 1 b.

normal levels and the loss in weight temporarily ceased. This suggests that tyrosine becomes an essential aminoacid if its conversion from phenylalanine is disturbed.

During the third week general aminoaciduria developed with involvement of some nine aminoacids, namely, serine, glycine, alanine, glutamine, glutamic acid, lysine, histidine, valine and the leucines. At the beginning of the fifth week the level of phenylalanine in the plasma and excretion of phenylalanine and phenylpyruvic acid in the urine began to rise again. The patient slowly but steadily lost weight and, though so far not unduly upset, started to vomit more frequently and seemed unwell. The findings were taken as evidence of increasing breakdown of body proteins due to phenylalanine deficiency and it was decided to add 0.8 g of phenylalanine daily to the diet in the form of 500 ml of milk. Unfortunately nitrogen balances were not practicable because of the child's constipation and repeated vomiting.

With the addition of the phenylalanine to the diet there was a rise of phenylalanine in the plasma to 34 and 28 mg per cent and in the urine to 200, 100, and 60 mg/24 hrs. The excretion of phenylpyruvic acid in urine also

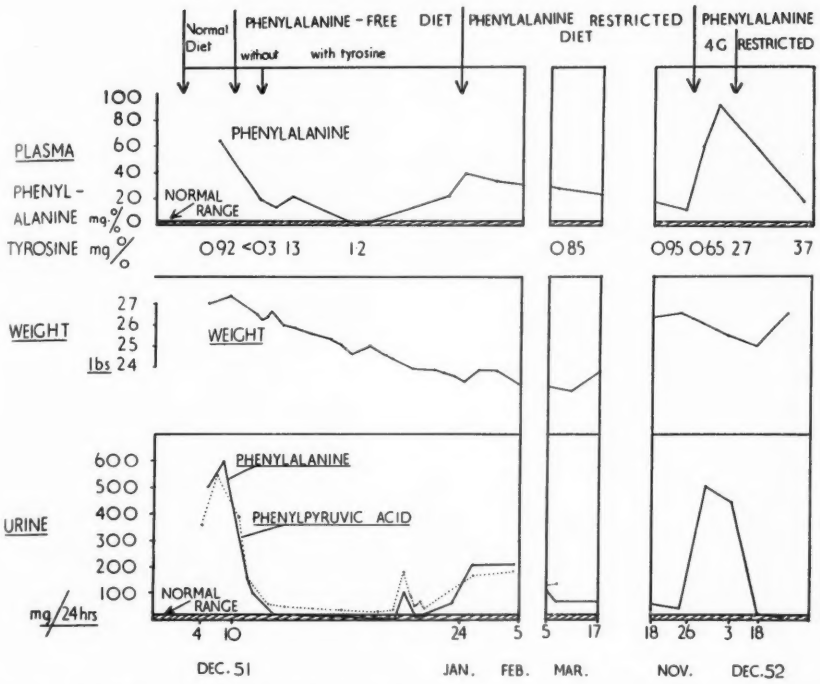

Fig. 2. The influence of a phenylalanine-free and a phenylalanine-restricted diet on the patient's biochemistry (see text).

rose to 178, 122, and 124 mg/24 hrs., but all these figures were well below the values on an unrestricted phenylalanine intake. The child gained weight satisfactorily and was sent home on a limited phenylalanine intake. Her condition was reviewed each week, when her mother came for the supply of phenylalanine-free casein hydrolysate.

During the next six months the child appeared to improve appreciably. Her eyes became brighter, she took more interest in her surroundings and in her food. She learned to crawl, to stand, to push chairs and to climb up on them. Her hair grew thicker and began to shine, and changed in a few weeks from a fair to a dark brown colour. Roughness and eczema of the skin disappeared, as did the mouse-like smell. Weekly $FeCl_3$-tests of the urine during this period were negative or showed only moderate green colouration which developed slowly and faded in 2–3 minutes. In 8 months she gained 2 pounds 4 ounces in weight. A critical assessment of the child's progress was, however, rendered difficult by her youth and her mental backward-

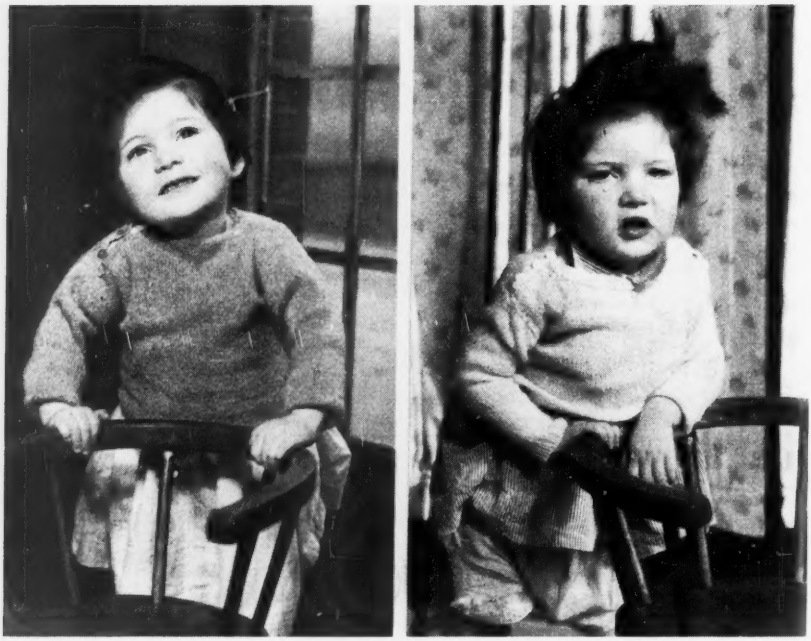

Fig. 3. The patient at 3 yrs. 1 mth. *Left*, much improved after eleven months on a phenylalanine-restricted diet (November 1952), *right*, four days later on 4 g L-phenylalanine daily. Rapid regression of her mental condition.

ness, which was still quite obvious, and also because some development was to be expected even without therapy.

We therefore decided to add a greater quantity of phenylalanine to the child's diet, for we considered that only if this caused a deterioration in the child's condition could a continuation of the phenylalanine-low diet be justified. Five g of L-phenylalanine were therefore added to each day's supply of phenylalanine-free casein hydrolysate. In order to obtain the mother's unprejudiced opinion we did not tell her of this change in the child's diet. When she returned a week later she was in tears and she came for the first time without her daughter, for the latter, she said, had lost in a few days all the ground gained during the previous ten months. Her daughter, within six hours of starting the fresh supply of "food", had begun to cry and to roll and bang her head just as she used to do. On the following day she had cried continually, her eyes had become heavy, she could no longer stand and she could scarcely crawl. The mother then discontinued the "food" as she was afraid a mistake had been made, and within a few days the child began to recover.

The child's reaction to phenylalanine was regarded as so important that, with the mother's consent, the child was readmitted to hospital and, after a period of observation, 4 g daily of L-phenylalanine was added to the diet. The change in the child's behaviour was impressive and dramatic and confirmed the mother's observations. Within twenty-four hours she became increasingly irritable and drowsy, her facial expression, particularly that of her eyes, became vacant and she lost interest in her food and surroundings. She developed facial eczema and salivated profusely. Her knee jerks became brisker, she became increasingly ataxic and vomited repeatedly, usually 2–3 hours after phenylalanine feeding. After six days she could no longer stand or crawl and so the additional phenylalanine was discontinued. Recovery was somewhat delayed, as the child contracted chicken-pox, but when discharged three weeks later she had almost completely recovered and has improved further at home. Fig. 3 records her appearance in good and bad phases.

When phenylalanine was added to the diet the plasma phenylalanine level rose from 12 to 90 mg%, the urine excretion of this aminoacid from 35 to 500 mg/24 hrs. (Figs. 1b and 2). The $FeCl_3$-reaction, which was negative before the test, gave a black-green reaction while the child was receiving extra phenylalanine. Two weeks after discontinuing the extra phenylalanine, the urinary excretion of this aminoacid had again dropped to 20 mg/24 hrs. and the blood level fell during the next few weeks to 28 and 19.5 mg%. At home, after further phenylalanine restriction in the diet, the phenylalanine blood content fell to the normal level of 1.2 mg% and the aminoacid disappeared from urine chromatograms.

Discussion

Our findings in a two year-old child with phenylketonuria suggest that the excess of phenylalanine or of its breakdown products has a deleterious action on mental function. No attempt, so far as we are aware, has hitherto been made to keep a phenylketonuric on a diet low in phenylalanine, probably because of the great practical difficulties involved.[1] Nor has any systematic feeding of phenylalanine to these patients been undertaken, though single doses have repeatedly been given in order to investigate the biochemical responses (PENROSE and QUASTEL, JERVIS 1938, JERVIS *et al.*, JERVIS 1947). Such tests resulted in a pronounced increase of phenylalanine in the blood and of phenylalanine and phenylpyruvic acid in the urine, but no untoward effects of these single test doses were mentioned.

In normal individuals it is unlikely that even prolonged administration of phenylalanine would produce a sufficient rise in phenylalanine plasma levels

[1] See addendum.

to cause toxic effects. Single phenylalanine doses have been given to normal subjects by PENROSE and QUASTEL, JERVIS (1947) and WOOLF (1953), but, in contrast to phenylketonuric patients, phenylalanine was rapidly transformed into tyrosine, even when 4 g were fed to a premature infant (WOOLF and EDMUNDS, WOOLF 1953).

We have given L-phenylalanine for 4 days to a normal child of 5 months and no untoward reaction was produced. The child was given 1 g of the aminoacid on the first day, 2 and 3 g on the second day and 4 g in a single dose on the two subsequent days. Weight for weight this child had three times as much phenylalanine as the phenylketonuric patient. The biochemical responses in this and in the phenylketonuric patient are given in Table 1. It will be seen that in the normal the phenylalanine blood level rose at the height of phenylalanine feeding only to 6.1 mg% as compared with 90.5 mg% in the phenylketonuric subject.

TABLE 1

Phenylalanine and tyrosine levels in a phenylketonuric patient and in a control before and during a phenylalanine feeding experiment (microbiological assay).

	Phenylketonuric patient		Normal control	
	Phenylalanine	Tyrosine	Phenylalanine	Tyrosine
Plasma mg%.				
Before phenylalanine feeding .	13.0*	0.7	1.4	1.7
During feeding of 4 g L-phenylalanine	90.5	2.7	6.1	2.9
Urine mg/24 hrs.				
Before phenylalanine feeding .	40*	5.3	4.2**	6.4
During feeding of 4 g L-phenylalanine	500	14.9	260	11.9

* On a diet low in phenylalanine.

** Estimated by microbiological assay. The other phenylalanine estimations in urine were done by chromatography (see text).

These findings do not indicate whether it is phenylalanine or one or more breakdown products which interfere with cerebral function. Neither phenylpyruvic acid nor phenyllactic acid have so far been detected in the blood of phenylketonuric patients with methods sensitive enough to show concentration of 10 mg% (JERVIS *et al.*) and 5 mg% (WOOLF 1953). The blood of phenylketonurics has not yet been examined for phenylacetic acid, but this is thought to be toxic to the central nervous system (SHERWIN and KENNARD, WOOLF 1951).

Of great interest is the recent discovery in the urine of our patients by Boscott of further abnormal metabolites such as p-hydroxy-phenylacetic acid, p-hydroxy-phenyllactic acid and o-hydroxy-phenylacetic acid. Their metabolic pathway and pathological significance in this disease are still obscure, but their presence suggests that the metabolic error in this disease is more than a simple inability of the tissues to convert phenylalanine to tyrosine.

The aim of the phenylalanine-poor diet must be to keep the phenylalanine blood level as near to the normal range as possible without producing a negative nitrogen balance. During the first few months on the diet at home weekly $FeCl_3$-tests of the patient's urine gave us some indication of the effectiveness of the phenylalanine restriction, but only when we began to estimate the phenylalanine in the plasma at frequent intervals were we able to ensure adequate dietetic control.

As a source of aminoacids we have preferred an acid casein hydrolysate to enzymatic preparations; the latter have an unpleasant taste and easily produce nausea. They also have the disadvantage of containing foreign material introduced in the process of hydrolysis, as well as a certain percentage of polypeptides, both sources of phenylalanine. Acid hydrolysates already have a low phenylalanine content, for phenylalanine, as well as tryptophane, cystine and tyrosine, is partly destroyed by the acid treatment (Block and Bolling). An alternative aminoacid source is a carefully balanced mixture of pure aminoacids, with the omission of phenylalanine, but the price of these is prohibitive.

The value of this phenylalanine-restricted regime in phenylketonuria can only be assessed by further trials. These are now being undertaken on children of different ages. Our present studies suggest that similar treatment does not benefit older children of low grade intelligence because the long continued interference with cerebral function will probably have led to permanent brain damage in these cases. Similarly older patients with galactosaemia and cretinism do not respond to appropriate treatment, but if treatment is started in early infancy improvement may be spectacular. By analogy, it is reasonable to presume that the best results of the dietetic treatment of phenylketonuria will be obtained if treatment is also started in infancy and particularly in the neonatal period; such babies could be detected in families where a sibling is known to have the disease.

We gratefully acknowledge the help and interest of Dr. W. C. Smallwood, Professor J. M. Smellie and Professor J. R. Squire. We are also grateful to Dr. L. I. Woolf, who first drew our attention to the technique of removing phenylalanine from casein hydrolysate and generously supplied us with a gift of phenylpyruvic acid and alpha-acetyl-amino-cinnamic acid. We wish to thank

the nursing staff at the Children's Hospital, Birmingham, for their help with the metabolic studies, Mr. J. G. WILLIAMSON, medical photographer to the Children's Hospital, for the illustrations, and Mr. B. T. RUDD and other members of the Biochemical Department for their careful and thorough work. The plastic apparatus for the urine collection was kindly prepared by Dr. E. DAVIES THOMAS and by Mr. N. WEBSTER from the Department of Dental Prosthetics, University of Birmingham. Messrs. Allen and Hanburys Ltd. have recently supplied us with a gift of phenylalanine-free casein hydrolysate.

Addendum: In a recent personal communication Drs. M. D. ARMSTRONG and F. H. TYLER from Utah University, Salt Lake City, have given us details of similar studies on three phenylketonuric children of 13 months, 4 years and 4 1/2 years of age. They were unable to obtain a phenylalaninefree hydrolysate and used instead a phenylalanine restricted diet in which the aminoacids were given in the pure form. They observed some very definite changes in behaviour in all three children. The 13 months old patient was maintained on the diet for 9 months, during which time her serum phenylalanine level was generally below 4 mg%. No definite regression was, however, observed when phenylalanine was finally returned to the diet, and the results of their experiments were regarded as equivocal.

Summary

Phenylketonuria is a not uncommon cause of mental deficiency (there are probably 1600 cases in Great Britain alone). On the supposition that the high level of phenylalanine or its breakdown products in the blood and cerebrospinal fluid might be responsible for the mental retardation in this disorder we have treated a two year-old child with a diet low in phenylalanine. The introduction of this diet was associated with an appreciable improvement in the patient's mental status and a fall in the level of phenylalanine in the blood and urine. When phenylalanine was again given in fairly large amounts there was an immediate and dramatic deterioration in the child's mental and biochemical condition. A similar phenylalanine intake produced no clinical reaction in a control child.

The main source of aminoacids in the diet was an acid casein hydrolysate which was specially treated to remove phenylalanine. The aim of the phenylalanine-poor diet was to keep the phenylalanine blood level as near the normal range as possible. The preparation of such a diet presents little difficulty if a phenylalanine-free casein hydrolysate is available. Its value in the treatment of other children is at present being investigated; it seems reasonable to assume that patients in the first two years of life will benefit most.

L'influence de l'absorption de phénylalanine sur les données chimiques et le comportement d'un enfant phénylcétonurique.

La phénylcétonurie est une cause relativement fréquente de déficit mental. (Il y en a, probablement, 1600 cas en Grande Bretagne seulement). En admettant que le taux élevé de phénylalanine, ou de ses produits de dégradation, dans le sang ou le liquide céphalo-rachidien puissent être responsables du retard mental qu'on trouve dans cette affection, nous avons administré à un enfant de deux ans, un régime pauvre en phénylalanine. Avec l'introduction de ce régime est apparue une amélioration sensible dans l'état mental du malade, en même temps qu'on notait une chute du taux de phénylalanine dans le sang et les urines. Lorsqu'on rendait de la phénylalanine en quantités importantes à l'enfant, il survenait une diminution immédiate des facultés mentales et une modification des conditions biochimiques. L'administration d'une quantité semblable de phénylalanine à un enfant normal n'a provoqué aucune reaction clinique. La principale source des aminoacides dans le régime institué a été un hydrolysat acide de caséine spécialement traité pour enlever la phénylalanine. Le but du régime a été de maintenir dans le sang un taux de phénylalanine aussi près que possible du taux normal. L'administration d'un tel régime ne souffre pas de difficultés, si on dispose d'un hydrolysat de caséine sans phénylalanine. Nous recherchons maintenant sa valeur pour le traitement d'autres enfants. Il semble logique de penser que les malades des deux premières années de la vie, sont ceux qui en profiteront le plus.

Der Einfluß von Phenylalaninzufuhr auf die Chemie und das Benehmen eines Kindes mit Phenylketonurie.

Schwachsinn geht nicht selten mit der Stoffwechselstörung der Phenylketonurie einher. In Großbritannien allein wird mit etwa 1600 solcher Fälle gerechnet. Ein zweijähriges idiotisches Mädchen mit Phenylketonurie wurde mit einer phenylalaninarmen Diät behandelt in der Annahme, daß vielleicht die in dieser Krankheit hohe Blut- und Liquorkonzentration von Phenylalanin oder von Phenylalaninabbauprodukten für den Schwachsinn verantwortlich ist. Unter der Diät wurde während der nächsten 8 Monate eine deutliche Verbesserung der geistigen Entwicklung des Kindes sowie ein Abfall des Phenylalaningehaltes in Blut und Urin beobachtet. Auf erneute intensive Phenylalaninzufuhr trat eine prompte und dramatische Verschlechterung der klinischen und biochemischen Befunde ein, während ein gesundes Kleinkind durch eine ähnliche Phenylalaningabe nicht beeinträchtigt wurde. Aminosäuren wurden in der Diät hauptsächlich in Form eines Säurecaseinhydrolysates zugeführt, das zwecks Entfernung von Phenylalanin besonders vorbehandelt worden war. Die phenylalanin-arme Diätbehandlung war darauf ausgerichtet, den Phenylalanin-Blutspiegel soweit wie möglich zu normalisieren. Steht ein phenylalanin-freies Caseinhydrolysat zur Verfügung, so bietet die Zusammenstellung der Diät wenig Schwierigkeiten. Ihr Wert in der Behandlung weiterer phenylketonurischer Kinder verschiedenen Alters wird derzeit untersucht, doch dürften Therapieerfolge im wesentlichen in den ersten zwei Lebensjahren zu erwarten sein.

La influencia de la fenilalanina en la química y conducta de un niño fenil acetonúrico.

La fenil acetonuria es una causa poco común de deficiencia mental (hay probablemente 1.600 casos en Gran Bretaña). En la suposición que el alto nivel de fenilalanina o de sus productos de descomposición en la sangre y el líquido cerebro espinal, puedan

ser responsables de un retardo mental, hemos tratado a una niña de 2 años con una dieta baja en fenilalanina. La introducción de esta dieta estaba asociada con una apreciable mejora en el estado mental del enfermo y una caída del nivel de la fenilalanina en la sangre y orina. Cuando la fenilalanina era dada nuevamente en grandes cantidades las condiciones mentales y bioquímicas del enfermo empeoraban en forma dramática e inmediata. Una dosis similar de fenilalanina no producía reacción clínica en el niño control. La fuente principal de aminoácidos en la dieta era un ácido caseínico hidrolizado que fué especialmente tratado para quitarle la fenilalanina. La finalidad de la dieta pobre en fenilalanina era mantener el nivel sanguíneo de la fenilalanina lo más próximo posible a lo normal. La preparación de esa dieta presenta poca dificultad si se dispone de un hidrolizado de caseina libre de fenilalanina. El valor en el tratamiento de otros niños está siendo investigado ahora; parece razonable pensar que enfermos en los dos primeros meses de vida beneficiarían con este tratamiento.

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CASE REPORTS

Di Guglielmo's Disease

Comments on a Case of Erythroleucemic Myelosis

by GRETA HEDENSTRÖM and NILS SÖDERSTRÖM

From the Children's Department of Falu lasarett, Falun, Sweden.
(Head: Dr. Bertil Hamne)

A. L., a girl, aged 14 years, was admitted to the Children's Department of Falu lasarett on July 24, 1952 (622/52). A month earlier she had had a sore throat and since then had felt tired and had been troubled by pains in her back. She had also suffered from obstipation and had vomited a few times. There had been several nasal and gingival bleedings and she had become thin and pale.

A cousin of the patient's mother was known to have had leucemia. On admission the girl was strikingly thin and pale with a yellowish colour but otherwise her general condition was fairly good. There was some enlargement of the cervical lymph nodes, and also, although less prominent, of the axillary and inguinal glands. The gingiva and the tonsils were free from pathological changes. The liver was moderately firm and its smooth rounded edge reached to the level of the umbilicus, while the spleen was felt about three fingers further down. The edge of the spleen was smooth, firm and slightly lobulated. Examination of the heart revealed a systolic murmur.

All over the body there were brown, raised spots of about the size of a pea.

The temperature was irregular, varying between 38° C and 39° C during the girl's stay in hospital. She was treated with iron and folic acid without any improvement and on Aug. 14, three weeks after admission, the temperature rose suddenly, she became severely dyspnoic and died within a few hours.

Myeloblasts and nucleated red cells predominated in the blood, most of the red cells being of a very immature and atypical kind.

Bone marrow (sternal puncture on July 25): A very cellular smear, the cytology varying in different parts; everywhere there is, however, a predominance of cells belonging to the erythropoietic system, normoblasts and more immature erythroblasts appearing in about equal amounts. In some areas groups of large erythroblasts, preferably called promegaloblasts are to be seen, but no typical megaloblasts.

Among the cells not belonging to the erythropoietic system the myeloblasts are definitely predominant, being mostly micromyeloblasts, some of them with an atypical nucleus. Promyelocytes, myelocytes, plasma cells and lymphocytes are very scanty. Megakaryocytes are lacking in the smear.

Considering the very heterogenous distribution of the cells, the following figures might give an idea of the composition of the marrow:

TABLE 1

Blood	Date					
	24/7	25/7	30/7	31/7	7/8	11/8
Hb %.	50		54		50	46
RBC mill./mm³	2.3		2.4		2.1	2.1
Nucleated RBC per 100 WBC	200		89		108	57
Reticulocytes. %	19.4			12.4	23.8	
Index.	1.08		1.13		1.19	1.09
WBC	27,000		90,000		58,700	70,000
Myeloblasts %	52		42		68	
Promyelocytes, % . . .	1		1		1	
Megalocytes, %	1		3		10	
Band forms, %	4		6		1	
Neutroph. granulocytes, %	16		33		12	
Eosinophil granulocytes, %	3		4		2	
Basophil granulocytes, %	3		1		0	
Lymphocytes, %	17		1		1	
Monocytes, %	1		5		1	
Thrombocytes	390,000	420,000				
Bleeding time		8 min.				
Clotting time		1½ min.				
Prothrombin index . . .		100				

Cells belonging to the erythropoietic system ..... 63 %
Myeloblasts ..... 25 %
Other cells (myelocytes etc.) ..... 12 %

The erythrocyte saline fragility test showed hemolysis beginning at 0.86 %, complete at 0.28 %.

The blood group was 0 Rh (+). No abnormal agglutinin. Coombs' test, direct and indirect, negative.

Serum iron was 67 γ %.

While the takata test was negative, the thymol test revealed 4.2 units and the urine contained a little urobilinogen.

The micro sedimentation rate was 2 mm hour.

A test meal revealed ordinary gastric acidity.

X-ray examination of the knee joints revealed nothing pathological.

At *autopsy* the pleural surfaces of both lungs and the pericardium were found to be covered with numerous yellow infiltrations the size of a pea. In the abdomen huge retroperitoneal masses were found penetrating into and surrounding the suprarenals and other retroperitoneal organs. The cut surface of the liver (3,175 g) was speckled and of a reddish brown colour, while the spleen (2,700 g) showed a deep red, somewhat greasy surface when cut.

Microscopical examination (Gellerstedt) showed cellular infiltration of the pituitary gland, the lungs, the myocardium, the spleen, the liver and the suprarenals. The bone marrow showed many types of cells, suggesting myeloid leucemia. The erythroblastic predominance was, however, very striking. There were multiple conglomerates consisting exclusively of more or less immature normoblasts and erythroblasts.

Discussion

It is a debatable question whether there exists a disease of the erythropoietic system corresponding to the leucemias of the leucopoietic one. It is tempting to use the word "erythremia" for such conditions, but many authors speaking of erythremia mean polycytemia vera or Vaquez' disease. It is, however, doubtful whether the leucemias and the polycytemias really are analogous conditions. Close relationship exists on the other hand between the leucemias and some other hyperplastic diseases of the erythropoietic system. DI GUGLIELMO who has described several cases of this group and established the existence of these maladies as a nosological entity, uses the term erythremia to define them. In order to avoid terminological confusion we have decided to call them di Guglielmo's disease.

di Guglielmo's disease is an elective hyperplasia of the erythropoietic system. The erythroblasts of the bone marrow, especially the most immature of them, are greatly increased and they occur in large numbers also in the blood, where counts of 20,000–40,000 erythroblasts per ccm are not exceptional. As in the leucemias the blood is thus flooded with immature cells but there is no excess of mature erythrocytes as is the case in polycytemia. On the contrary, a progressive anemia (hypo- or normochromic) is a regular feature of the clinical picture.

The analogy with certain types of (acute) leucemia is still more marked by the presence of definitely abnormal erythroblasts (for instance those with an obvious inequality between the maturity of the nucleus and that of the cytoplasm). DI GUGLIELMO calls such cells *paraerythroblasts*. Another feature of interest is the predominance of immature erythroblasts, while more mature cells of "normoblast" type are more scanty. For this phenomenon DI GUGLIELMO introduces the term "hiatus erythremicus".

There is always a widely distributed extramedullary erythropoiesis, for example in the spleen, the liver, the pancreas, the suprarenals and the lymph nodes. It is difficult to say if this is a vicarious hemopoiesis, comparable with what is found in osteosclerosis and other diseases of that kind, or if it is a phenomenon analogous with the leucemic infiltrations in leucemia.

Usually the liver and spleen are considerably enlarged. The mucous membranes are never damaged as they tend to be in leucemia. Bleeding, for instance epistaxis or purpura, may occur, especially in cases with thrombocytopenia. Most patients have irregular fever.

DI GUGLIELMO's first case and most cases described since have died after a short clinical course in very much the same way as do patients suffering from acute leucemia. Later on, however, DI GUGLIELMO described cases, where the patients had been ill for several years. Here the analogy with chronic leucemias is obvious.

While the erythremia may run an acute or a chronic course as an isolated disease, it can also be found combined with leucemia. In such cases the term erythroleucemia seems to be generally accepted. Here the clinical course is mostly acute. If the erythroleucemia is in its turn combined with thrombocytemia, DI GUGLIELMO

and other Italian and French writers speak of "panmyelosis", thus indicating that the disease concerns the hemopoietic system as a whole.

The prognosis of the erythremias appears always to be bad and to be uninfluenced by any kind of therapy.

In one case, running a chronic course, MALLARMÉ after repeated transfusions with stored blood got quite a normal blood picture. Fresh blood was not tolerated. It would seem, however, that this case had not been followed for any considerable time after the treatment. It is consequently difficult to draw any definite conclusions from a single observation like this.

di Guglielmo's disease is rare and only about 80 cases have been described as yet. Erythroleucemias seem to be even less frequent than the isolated erythremias. The disease is not hereditary. Cases have been reported from most parts of the world, and often the patients have been children.

The main difficulty in diagnosis is probably the differentiation of di Guglielmo's disease from some cases of acquired hemolytic anemia with very active erythropoiesis and high erythroblast-normoblast-counts in the blood. Considering this difficulty some authors refuse to accept di Guglielmo's disease as a separate entity. Important diagnostic points in this connection are the specific "leucemoid" traits in cases of di Guglielmo's disease: the presence of abnormal erythroblasts — paraerythroblasts —, of hiatus erythremicus, and the persistance of excessively high erythroblast counts in the blood.

In erythroleucemia the diagnosis is in a way easier as the leucemia indicates the nosological nature of the disease. Here the difficulty is in proving that the affection of the erythropoietic system is a primary condition corresponding to and analogous with the coexistent leucemia.

It is important to realise that in leucemia some kind of hemolytic reaction can often cause a secondary reactive hyperplasia of the erythropoietic system. Erythroblasts, eventually found in a case of leucemia, may also be looked upon as emanating from hemopoietic centres outside the bone marrow, these centres having been brought into existence by the leucemia in very much the same way as the extramedullary centres seen in cases of carcinosis of the bones. According to DI GUGLIELMO the erythroblasts increase contemporaneously with an improvement of the hemoglobin values in cases of reactive hyperplasia, while in erythremia the growing erythroblastic predominance coincides with the development of the anemia. The conclusive erythremic trait is however the marked degree of erythroblastic predominance and immaturity.

In our case the presence of leucemia may be regarded as unquestionable (leucemic myeloblast count in the blood, leucemic infiltrations). The myeloblasts were, however, less frequent both in the blood and in the bone marrow than were immature cells belonging to the erythropoietic system, some of them being very atypical. In all smears the number of erythroblasts was definitely higher than the total number of all other cells, and the blood contained 15,000 to 40,000 erythroblasts per ccm.

We think this patient must have had a genuine erythroleucemia with the erythropoietic and the leucopoietic systems affected in the same way. The one alternative in our opinion is a myeloblastic leucemia with hemolytic reaction. Although hemolytic signs were undoubtedly present, the erythroblastosis was too predominant, and the atypia of the cells too obvious to originate from a normal erythropoietic system.

Summary

A disease is described in a girl aged 14 years, in which an acute myeloblastic leucemia was combined with a probably analogous affection of the erythropoietic system. There were definitely leucemic myeloblast counts in the blood, but there, as well as in the bone marrow, the myeloblasts were outnumbered by mostly very immature erythroblasts, many of which were atypical. A hyperchromic anemia and signs of hemorrhagic diathesis were present. The clinical course of the disease was that of a very acute leucemia and the patient died after three weeks' observation. It is considered to be a case of genuine erythroleucemic myelosis (erythroleucemia).

Maladie de di Guglielmo. Commentaires sur un cas de myélose érythroleucémique.

Chez une fille de 14 ans chez laquelle une leucémie aiguë myéloblastique coincidait avec une affection probablement analogue du système érythropoétique. Il y avait des myéloblastes leucémiques dans le sang, mais là était également dans la moëlle osseuse, les myéloblastes étaient dominés par des érythroblastes très jeunes dont beaucoup présentaient un caractère atypique. La malade présentait des signes d'anémie hyperchrome et de diathèse hémorragique. L'évolution clinique fut celle d'une leucémie aiguë et la malade mourut au bout de 3 semaines d'observation. Nous pensons qu'il s'est agit là d'un cas de véritable myélose érythroleucémique (érythroleucémie).

Über die di Guglielmo-Krankheit. Bemerkungen über einen Fall von erythroleukämischer Myelose.

Bei einem 14-jährigen Mädchen wird ein Krankheitsbild beschrieben, bei welchem eine akute Myeloblastenleukämie mit einer wahrscheinlich analogen Reaktion des erythropoetischen Systems kombiniert war. Dabei war eine begrenzte Zahl von leukämischen Myeloblasten im peripheren Blut, aber sowohl hier als auch im Knochenmark wurde die Zahl der Myeloblasten von meist unreifen Erythroblasten — viele von ihnen waren atypisch — übertroffen. Eine hyperchrome Anämie und Zeichen einer hämorrhagischen Diathese lagen vor. Der klinische Verlauf der Krankheit glich dem einer sehr akut ablaufenden Leukämie und die Patientin starb nach einer 3-wöchigen Beobachtung. Wir nehmen an, daß es sich um einen Fall von genuiner erythroleukämischer Myelose (Erythroleukämie) handelte.

Enfermedad de di Guglielmo. Comentarios sobre un caso de mielosis eritroleucémica.

Se describe una enfermedad en una niña de 14 años de edad, en la cual se combinó una leucemia mieloblástica aguda con una probable infección análoga del sistema eritropoyético. Había valores definidos de mieloblastos en la sangre, pero en ésta, igual como en la médula ósea, los mieloblastos fueron excedidos en número por eritroblastos, la mayoría de los cuales eran inmaduros siendo mychos de ellos atípicos. Se presentaron una anemia hipercrómica y signos de diatesis hemorrágica. El curso clínico de la enfermedad fué el de una leucemia muy aguda y la paciente falleció a las tres semanas de observación. Nosotros creemos que fué un caso de mielosis eritroleucémica genuina (eritroleucemia).

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Acute Methaemoglobinaemia Caused by Aniline Dye Intoxication

Report of a Case

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During recent years, a number of reports have been published of intoxication accompanying methaemoglobinaemia in infants. In many cases, the cause was traced to well-water containing nitrites used to dilute cow's milk mixtures (1, 3, 5, 9, 12). In other cases, symptoms of intoxication appeared in infants whose diapers were marked with aniline ink (1, 4, 8, 13, 14). In both groups, the course of the illness may be regarded as subacute.

Few reports of such acute intoxications are found in the literature. The following case of acute methaemoglobinaemia as a result of aniline dye intoxication therefore appears to be of interest.

The patient was a boy (Hospital record No. 78/53), aged 2¾ years, who earlier had been in good health. He was admitted to our hospital three hours after having drunk "a small mouthful" from a bottle labelled "Marking Ink". Immediately afterwards, he was given a glass of milk. About 2½ hours later, his parents noticed that his face was an ashen-grey colour, he staggered and seemed mentally confused.

On admission to hospital, the pale, yellowish-brown colour of his skin was striking. He was dry and warm, with obvious dyspnoea; the heart rhythm was rapid but regular. The systolic blood pressure was 80 mm Hg. When stimulated, he reacted adequately to pricks, but was otherwise somnolent. Oxygen was administered and gastric lavage undertaken immediately; the stomach contents were yellowish-brown. When a saphenous vein was exposed for drip transfusion, the patient's blood was found to be mahogany-coloured. The ECG showed definite signs of anoxaemia. His general condition improved under continuous oxygen therapy and drip transfusion of blood. The cyanosis became increasingly bluish-red, then paled and was no longer visible after 36 hours. During this time the patient was given altogether 925 cc of blood; 575 cc were given during the first 5½ hours and the remainder as an exchange transfusion about 12 hours after admission. The ECG returned to normal three days later. The patient was sent home in good condition nine days after admission. Examination in the Outpatient Department two weeks later disclosed nothing abnormal.

Spectroscopic examination of a blood specimen (Josephson) taken in connexion with the exchange transfusion showed a slight but definite band of methaemoglobin.

Among the substances that have caused intoxication in children owing to the formation of methaemoglobin are the sulphonamide group of drugs (5, 9, 17), aniline compounds (1, 2, 4, 5, 7, 8, 9, 13, 14, 15), nitrobenzene (5, 11), nitrites in well-water (1, 3, 5, 9, 12), bismuth subnitrate given for gastro-intestinal disturbances (1) or as X-ray contrast (5) and potassium chlorate (5, 9).

Methaemoglobin does not seem to be toxic in itself, but it causes damage owing to the anoxaemia which arises in the tissues and which is reflected in the patient's symptoms, i.e., dyspnoea, tachycardia, somnolence and, in more severe cases, convulsions. The pale brown cyanosis and the mahogany colour of the blood are a direct effect of the methaemoglobin and may well be regarded as cardinal symptoms. If the organism can be freed from the toxic substance, the methaemoglobin is spontaneously converted into normal haemoglobin. This reversible process is not completed until after about 36 hours (5, 16) but it may be hastened by the administration of a reducing substance. The mechanism of action of the reducing substances on methaemoglobin still appears to be hypothetical, and no uniform explanation is found in the literature.

The majority of authors have used methylene blue for the treatment of methaemoglobinaemia, the dosage being 1–2 mg/kg of body weight, injected intravenously in 1 per cent solution. In a few cases, cyanosis has been reported to disappear extremely rapidly, even within 10 to 15 minutes (9, 10, 17). Other authors have expressed the opinion that the effect of methylene blue is so good when given by mouth, that it should initially be given by this route in order to avoid the time lag involved in the preparation of a solution for parenteral administration. The dose should then be 10 times that given intravenously (1, 10, 16).

It has been pointed out in some quarters that methylene blue in itself forms methae-

moglobin and thus causes further blocking of the free haemoglobin (3, 5, 11) although, for some unknown reason, methaemoglobin in this form appears to have no injurious effects (5). However, in view of this property of methylene blue, a number of authors have suggested the substitution of thionine. Like the closely related methylene blue (tetramethyl-thionine) it is a phenothiazonium derivative. Thionine appears to be less toxic and has, in addition, a reducing capacity that is stated to be five times greater that of methylene blue (5, 6, 11). The dosage of thionine suggested is the same as that of methylene blue (12) or one-fifth of this dose (11).

Several authors have stated that oxygen therapy is of comparatively little value (9, 10, 12, 13).

In one case, a transfusion of packed cells was given, but was stated to have been ineffective (16). Another author (13) made an exchange transfusion in a case with severe intoxication, with good results. According to another report (2) treatment confined to blood transfusion and oxygen therapy—as in our case—resulted in satisfactory recovery.

Ascorbic acid, which was used earlier, is now stated to be less suitable, owing to its slow action (4, 10, 16).

A study of the literature thus shows that a specific form of therapy in methaemoglobinaemia has become established during recent years. A summary of the views on the treatment would therefore seem warranted.

If the poison has been taken by mouth, and the patient is admitted to hospital within the period during which the substance may be assumed to be present in the stomach—i.e., within three to four hours—the following scheme of therapy appears to be suitable:

1. Gastric lavage, possibly with physiological saline solution, and administration of carbon and magnesium sulphate. (Excessive gastric lavage with water should be avoided, owing to the risk of "water intoxication" (15).)
2. Oxygen therapy.
3. Stimulation.
4. *Thionine:* 10 cc intravenously and 10 cc intramuscularly, both in 0.2 per cent solution (adult dose). If thionine is not available (no commercial preparation can at present be obtained in Sweden) *methylene blue* is given: 1–2 mg/kg of body weight intravenously in 1–2 per cent solution with physiological saline or 5 per cent glucose solution. If considerable time is required for the preparations for parenteral therapy, 10 times the aforementioned dose of methylene blue may be given by mouth first.

(It is then suitable, in order to avoid overdosage, to use a 1 per cent solution, and to calculate the dose on the basis of 10 mg/kg of body weight for oral administration and 1 mg/kg of body weight for intravenous therapy.)

5. Blood transfusion; if necessary, in the form of an exchange transfusion.

If traces of aniline are found on the skin, they are removed with, for example, 70 per cent alcohol. Drenched clothes are removed, in view of the risk of absorption by the skin (cf. intoxications caused by diapers marked with aniline ink).

Summary

A case of acute methaemoglobinaemia caused by the ingestion of marking ink is described. A short survey is given of the relevant literature on the causes of methaemoglobinaemia, the clinical picture and the various therapeutic methods. A suitable scheme of treatment is suggested.

Méthémoglobinémie aigüe provoquée par une intoxication par l'aniline.

L'auteur décrit un cas de méthémoglobinémie aigüe provoquée par l'ingestion d'encre à marquer. Il donne ensuite un court aperçu de la littérature se rapportant aux causes de la maladie, à son aspect clinique et aux différentes méthodes thérapeutiques. Il indique enfin un schéma de traitement approprié.

Akute, durch Anilinfarbenintoxikation verursachte Methaemoglobinaemie.

Es wird über den Fall einer akuten Methaemoglobinaemie berichtet, die nach dem Verzehren von Zeichentinte auftrat. Ein kurzer Überblick über die Ursachen der Methaemoglobinæmie, ihr klinisches Bild und die verschiedenen therapeutischen Methoden, wird aus der verfügbaren Literatur gegeben. Ein geeignetes Behandlungsschema wird angegeben.

Metahemoglobinemia aguda causada por intoxicación con colorante de anilina.

Un caso de metahemoglobinemia aguda por ingestión de tinta de marcar. Resumen de la literatura de las causas, del cuadro clínico y tratamiento de la metahemoglobinemia. Un cómodo esquema de tratamiento es sugerido.

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Endocardial Fibroelastosis in Infancy

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Introduction

Endocardial fibroelastosis is a noninflammatory change of the endocardium, occurring most frequently in the left side of the heart and often accompanied by cardiac enlargement. The disease is not mentioned in some standard textbooks of pediatrics, but it does not seem to be uncommon—in fact, some authors consider it to be one of the commonest types of fatal heart disease of infancy (BLUMBERG and LYON).

During recent years, a number of publications on the subject have appeared, especially from the United States (EDMONDS and SEELYE, COLLIER and ROSAHN, HILL and REILLY, LEWIS (1951); BLUMBERG and LYON, ADAMS and KATZ (1952).

A disease of adult life which pathologically seems to be quite similar to endocardial fibroelastosis in infancy has been described (GRAY).

Three cases of endocardial fibroelastosis are reported below.

Nomenclature

The disease was formerly believed to be infectious and was described under the name of *fetal endocarditis.*

Endocardial fibrosis (BONHAM-CARTER, SWYER and PUGH), *endocardial fibroelastosis* (WEINBERG and HIMELFARB; HILL and REILLY; COLLIER and ROSAHN), *endocardial dysplasia* (PRIOR and WYATT), *prenatal fibroelastosis* (STADLER, REID and FRIEDMAN), *endomyocardial sclerosis and hypertrophy* (POTTER), and *endocardial sclerosis* (COSGRAVE JR. and KAUMP; CRAIG; BLUMberg and LYON) are terms which in most cases seem to cover the same pathological picture. Some of the previously reported cases are to be sought under the name of *congenital idiopathic cardiac hypertrophy* (WEISMAN).

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Pathologically, the disease is characterized by marked cardiac enlargement, the weight of the heart being often 2–3 times the normal average, and by congestive changes in other organs. On opening the heart, the most characteristic finding is a whitish thickening of the endocardium, involving larger or smaller portions of the cardiac chambers or, perhaps, generalized. Polypoid vegetations on the valves and concurrent hypertrophy of the myocardium are often observed. Frequently, there are other malformations, such as coarctation of the aorta, patent ductus arteriosus, valvular changes and abnormal coronary vessels, e.g., the left coronary artery may arise from the pulmonary artery. The endocardial and valvular thickenings may vary in extent, but are most frequently found in the left side of the heart. Endocardial changes without involvement of the valves may occasionally be seen (BLUMBERG and LYON).

Histologically, the disease is principally characterized by an increase in the fibroelastic tissue and ground substance of the endocardium, which may sometimes emit processes into the underlying myocardium. This is usually hypertrophied with hyperchromatic nuclei of varying size. Occasionally, slight fibrosis and degeneration or small calcifications are seen in the myocardium. There may be slight infiltration of leukocytes in the endocardium, but otherwise there are no histological signs of infection.

HILL and REILLY performed detailed histological studies on one case. They found fibrinoid precipitates in the ground substance of the valves and endocardium and obtained metachromatic staining reactions with toluidine blue and other similar stains. They expressed the view that the precipitates were mucopolysaccharides such as are seen in the collagen diseases (ALTSCHULER, KLEMPERER), and that fibroelastosis was related to the collagen diseases. No other investigators seem to have observed these fibrinoid precipitates, and HILL and REILLY's claim that the material observed is polysaccharide in nature is based exclusively on fairly capricious and rather unspecific metachromatic staining reactions, and they did not attempt to demonstrate the presence of polysaccharides by MCMANUS' specific periodic acid stain.

The etiology of the disease is still obscure. In view of the young age of the patients and the duration of the disease, its cause must be presumed to be of antenatal origin. Formerly, the disease was believed to be infectious—a fetal endocarditis. The fact that histological evidence of inflammatory processes have never been revealed speaks strongly against such an assumption.

A great number of various factors have in the past been suggested as the cause (see JOHNSON).

In recent studies the condition is interpreted as a form of congenital heart disease of unknown etiology. It may be a developmental error of mesenchymal

tissue and should, perhaps, be placed in the category of a congenital cardiac malformation (HILL and REILLY). WEINBERG and HIMELFARB, who encountered the disease in two siblings, spoke of a hereditary developmental defect. Also ULLRICH, who observed the condition in two identical triplets, believed that it might be attributed to some genetic factor.

JOHNSON expressed the opinion that fibroelastosis is due to anoxia of the myocardium. In an analysis of 23 cases, he found either congenital malformations or abnormal coronary vessels, which might explain the supposed anoxia. Some other writers who reported cases with origin of the left coronary artery from the pulmonary artery found pronounced fibrosis of the endocardium (GASUL and LOEFFLER, FISHER and LLOYD, MCKINLEY, ANDREWS and NEILL). This observation provides suggestive evidence in favor of the correctness of JOHNSON's theory. Virus infections in the mother during the first months of pregnancy may be mentioned as a possible cause, although no proof of such an etiology is available.

Clinical Manifestations

A diagnosis of endocardial fibroelastosis cannot be established with certainty during life. The clinical diagnosis can only be tentative. Recently, ADAMS and KATZ and BLUMBERG and LYON emphasized the possibilities of making a clinical diagnosis, while LOGUE and HURST especially discussed its differential diagnosis from rheumatic fever in the first few years of life.

ADAMS and KATZ discussed the diagnosis on the basis of 21 cases, while BLUMBERG and LYON (1952) reviewed some of the clinical features of the disease in 25 children observed over a five-year period and added 69 cases collected from the literature.

Among these 94 children, symptoms were noticed in 36 % before they were 2 weeks of age, and in 65 % the disease occurred before the age of 6 months. As 91 % of the children died before the age of 2 years, the disease is distinctly one of infancy; 51 % died within the first two weeks after the onset of symptoms; 29 % within two days. According to ADAMS and KATZ, the duration of the disease may vary within wide limits; in the severest cases it may cause sudden death, whereas patients with only mild symptoms may survive.

Even though the symptoms are often not characteristic at first—respiratory disorders and digestive symptoms—certain features nevertheless seem to be suggestive of the disease.

In some of the 94 children the symptoms had been noted from birth, with remissions and recurrences, and in these cases another diagnosis had often been suggested previously. According to BLUMBERG and LYON, the symptoms fall into two distinct groups. The first group comprises infants under 6 months

of age who have been in apparently good health until suddenly severe dyspnea, cough, tachycardia and vomiting develop. The other group exhibits similar symptoms but of a milder degree, with periods of remission and apparent recovery. In the patients belonging to the latter group the symptoms began during the first two years of life. Many of the patients had digestive symptoms, vomiting, anorexia, and diarrhea.

The most frequent symptom was cardiac enlargement, which was present in 94 % of the 94 infants. Dyspnea was present in 74 % and cyanosis in 65 % (in 47 % only in the terminal stage or intermittently). Liver enlargement was seen in 38 %, and murmurs were reported in 25 %, usually described as a soft systolic murmur at the apical area.

The most frequent abnormality in the electrocardiograms was depressed, inverted or diphasic T waves, but the pathological changes were very variable.

Roentgen examination revealed a markedly enlarged heart, primarily of the left side. In some cases the heart was globular in configuration and so large that pericardial or pleural effusion was suspected. In one patient with pronounced fibroelastosis of the left ventricle and auricle PREC and CASSELS found by angiocardiography a marked delay in outflow of Diodrast from the left ventricle, but no limitation of diastolic filling of the ventricle.

The localization of the disease seems to be of only minor importance for the type of symptoms. In all the 25 cases observed by BLUMBERG and LYON, the disease was located in the left side of the heart; in seven of them pathological processes were also observed in the right side. In all the cases reported by ADAMS and KATZ the disease was located in the left side of the heart; in two of the patients involving the right side also.

Differential Diagnosis

As already pointed out, an unquestionable diagnosis of endocardial fibroelastosis cannot be made clinically, but it may be rendered likely if other cardiac disorders can be ruled out. In the presence of heart murmurs the more common congenital malformations require differentiation; if murmurs are absent, myocarditis should especially be considered in the differential diagnosis. Obviously, the presence of concurrent congenital lesions will add to the diagnostic difficulties.

LOGUE and HURST emphasized the difficulties encountered in the differential diagnosis of endocardial fibroelastosis from rheumatic fever. The following observations should be in favor of a diagnosis of endocardial fibroelastosis: (1) absence of murmurs in congestive heart failure; (2) cardiac dilatation and congestive heart failure during the first six months of life (if these findings are not referable to more common congenital defects); (3)

the combination of cardiac enlargement with congestive heart failure and coarctation of the aorta. On the other hand, the presence of other rheumatic symptoms, a high sedimentation rate, and pericarditis are in favor of a diagnosis of a rheumatic infection. Long survival and supervening aortic insufficiency should also point to the latter diagnosis.

Report of Cases

Case 1.—A girl (158/52), aged 5 months, was admitted to the Pediatric University Clinic of Aarhus Municipal Hospital on February 6, 1952.

The mother, aged 27, had been in good health during the pregnancy and had never had any miscarriages.

The patient was the youngest of three children; the other two were in good health. Delivery had been normal; no asphyxia. Birth weight 3200 g; length 50 cm; initial weight loss 400 g. The baby had been breast-fed for the first 7 weeks, but had failed to gain. She was then fed on a formula of undiluted acid milk, but as weight gain was still unsatisfactory, she was admitted to a regional hospital at the age of 3 months. As regurgitation and vomiting had occurred ever since birth, she was treated with Eumydrine. Vomiting became less frequent and the weight increased to 3800 g, but as she again failed to gain weight, she was transferred to this clinic. On admission the patient was emaciated (weight 3290 g, length 55 cm) and showed considerable mental and physical retardation. The thorax was slightly distended; no thrill; the heart beat could not be felt. The heart sounds were heard over the entire anterior surface of the thorax, everywhere with a loud systolic murmur. Auscultation did not reveal any rales or dullness. There was no dyspnea or cyanosis.

Abdomen: The liver was felt two fingerbreadths below the costal margin. The spleen was not palpable. No gastric peristaltic waves were seen. No pyloric tumor was felt, and there was no gastric retention. The baby took feedings poorly and had to be fed by gavage. In spite of occasional vomiting, the baby gained 410 g during the first 17 days in hospital.

On Feb. 23, the patient had a common cold and began to cough, and fever developed. Penicillin therapy resulted in a transitory fall in temperature, but the condition deteriorated, still without dyspnea or cyanosis, and death ensued at the age of 6 month.

Laboratory examinations.—The Wassermann reaction in blood from the umbilical cord and the tuberculin test were negative. Gelatin film test for stool trypsin showed normal proteolytic activity. Electrocardiograms showed regular action, heart rate 150, and right axis deviation. The conduction time, ventricular complexes, and T waves were normal.

Roentgenograms taken on Feb. 8 revealed a heart of normal size and form; no displacement of the esophagus was observed. The pulmonary markings were exaggerated, with scattered patches of increased density. A month later, the heart showed no change but the pulmonary involvement had become more pronounced.

Autopsy.—The body was that of an extremely emaciated child without external developmental defects.

Heart: The pericardium contained a few ml of clear serous fluid, but there was no thickening. The heart weighed 39 g and was moderately enlarged due to hypertrophy and dilatation, especially of the right ventricle and auricle. The great vessels were normal and the ductus arteriosus was obliterated. The foramen ovale was widely

Fig. 1. Markedly thickened pulmonary cusp (case 1).
Fig. 2. Normal pulmonary cusp from 8-month-old child.

open, but otherwise no developmental anomalies. The ostia seemed to be of normal width, but the pulmonary valves and, to a smaller extent, also the mitral cusps were thickened, and the pulmonary valves presented as rounded, whitish pads with a smooth endocardial lining. The auricular and ventricular endocardium did not reveal any abnormalities; particularly, no definite thickening was present. Lungs: The cut surface showed edema and congestion, and small scattered infiltrations and airless areas were present. Liver: Acute congestion. The rest of the autopsy was not relevant.

Histological examination.—Sections of the pulmonary and mitral valves showed marked thickening with increase of the fibroelastic tissue, but there were no inflammatory changes and no vascularization (Fig. 1). Section of the myocardium showed normal conditions; there were no inflammatory changes, degeneration or fibrosis.

Case 2.—A girl (1179/52), aged 7 months, was admitted to the Medical Department of Vejle County Hospital. She was the younger of two children. The mother had been in good health during the pregnancy; her Wassermann reaction was negative. The father suffered from chronic bronchitis.

Birth weight 3200 g; the infant had been bottle-fed without vitamin addition.

At a prophylactic public health examination shortly before the age of 7 months, the physician reported that the child looked pale and poorly. She was vaccinated against pertussis, because the elder sister was suffering from that disease.

A fortnight later, the doctor was sent for, because the child had had some atypical coughing attacks during the last two days. Examination revealed marked cyanosis of the lips and cheeks, marked dyspnea, and wheezy breathing. Temperature 36° C; the child was at once sent to hospital.

Fig. 3. Hypertrophic and dilated left ventricle, with whitish, thickened endocardium and normal aortic cusps (case 2).

Fig. 4. Normal left ventricle from 8-month-old child.

On admission, the patient was restless and had slight cyanosis of the lips; otherwise nothing abnormal; temperature 37.5°. Auscultation of the heart was difficult because the infant was crying, but normal conditions were believed to be present. The child was kept under observation; she had a couple of atypical coughing attacks, and 3½ hours after admission the temperature had risen to 38.5°. Half an hour later the infant was found dead.

Autopsy.—The body was that of a well-developed and normally nourished child without external developmental defects.

Heart: The pericardium was normal without fluid. The heart weighed 121 g and was markedly enlarged, almost globular in configuration, with pronounced hypertrophy and dilatation, particularly of the left ventricle. The great vessels were normal;

Fig. 5. Hypertrophic and dilated left ventricle, with whitish, thickened endocardium and markedly swollen aortic cusps (case 3).

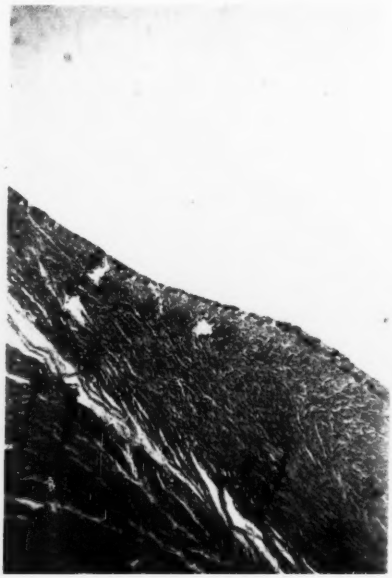

Fig. 6. Section through the endocardium and myocardium from the left ventricle showing the markedly thickened endocardium (case 2).

Fig. 7. Section through the endocardium and myocardium of the left ventricle from a *normal* heart showing the thin and delicate endocardium.

the ductus arteriosus was obliterated, and there were no septal defects. The endocardium of the left ventricle was markedly thickened and whitish, especially on the interventricular septum (Fig. 3). The endocardium of the left auricle was also slightly thickened, but the right side of the heart showed normal endocardium, and there was no thickening of the valves.

Lungs: Abundant amounts of mucopurulent secretion were present in the bronchial branches, and small atelectatic areas were revealed in the posterior portions of the lungs. On the cut surface, edema and congestion were seen.

The liver, spleen and kidneys showed distinct acute congestion; the rest of the autopsy was not relevant.

Histological examination.—Sections of the interventricular septum showed marked thickening of the endocardium of the left ventricle; the thickened tissue was made up of hypocellular fibroelastic connective tissue without inflammatory changes (Fig. 6). Fine processes of connective tissue ran from the endocardium into the subjacent layer of the myocardium, which was hypertrophied with slight degenerative changes in the upper layers. There were no inflammatory changes in the myocardium.

Various sections of the lungs showed edema and congestion and small scattered infiltrations of polymorphonuclear leukocytes.

Sections from the liver, spleen and kidneys showed marked congestion, and slight fatty degeneration of the liver cells was observed.

Case 3.—(This case has previously been published by W. MUNCK under a diagnosis of chronic endocarditis of the aorta and the mitral valves in a paper on congenital heart disease as the cause of sudden death.)

The mother had been in good health during the pregnancy. The child, a boy, was born 4 weeks prematurely. He died without preceding symptoms at the age of three days.

Autopsy showed polypoid vegetations on the aortal and mitral valves and whitish thickening of the endocardium of the left ventricle (Fig. 5). The heart was hypertrophied. The liver showed chronic congestion, with a marked nutmeg pattern on the cut surface.

Grossly, the cardiac changes were thus identical with those of endocardial fibroelastosis; a renewed examination of the histologic sections revealed an increase in the fibroelastic tissue of the endocardium, but no signs of inflammation.

Discussion

In an attempt to evaluate the described thickening of the endocardium and the valves with special reference to a possible collagen disease (HILL and REILLY), the post-mortem material from cases 1 and 2 was studied by various special staining methods. The ordinary staining methods with hematoxylin-eosin and van Gieson–Hansen stain were supplemented with toluidine blue, methylene blue, mucicarmine, orcein (elastic fiber stain), and the McManus periodic acid stain.

The thickened valves and endocardium were both made up of a hypocellular connective tissue with normal collagen fibers and with a varying admixture of elastic fibers. There were no fibrinoid precipitates in the ground substance, and staining with toluidine blue and methylene blue did not reveal any metachromasia of the ground substance or the connective tissue fibrils. Nor did the McManus stain show any abnormal accumulation of polysaccharides; consequently, there did not seem to be any evidence in support of an inclusion of these two cases among the collagen diseases.

The origin of the coronary arteries was normal in all three cases, but their further course was not studied.

In the three cases reported here the diagnosis was not established until the heart was examined histologically. In case 3 death occurred quite unexpectedly, and in case 2 a few hours after admission, so that there was no possibility of making the diagnosis during life in these two cases.

Would it have been possible to establish the diagnosis during life in case 1? Dyspepsia and failure to thrive were here the most conspicuous symptoms. The presence of a loud murmur over the heart and liver enlargement aroused suspicion that the cause of these complaints might be of cardiac origin. The diagnosis had to be one of congenital heart disease of uncertain type. The symptoms did not justify even a tentative diagnosis of endocardial fibro-

elastosis, especially because the most common sign in this disease, cardiac hypertrophy, was missing. The case was atypical, the changes being located exclusively in the right side of the heart.

However, even in the most typical cases the clinical symptoms may be so atypical that only a probable diagnosis of endocardial fibroelastosis can be suggested.

However, even such a suggestion may serve as an incitement to a closer examination of the endocardium, without which the pathological changes will undoubtedly often pass unrecognized.

Summary

Endocardial fibroelastosis was formerly interpreted as a fetal endocarditis, but has later been described under many different names. The etiology is obscure, but the disease is now believed to be a developmental defect. There is an increase in the fibroelastic tissue of the endocardium, usually located in the left side of the heart. Considerable enlargement of the heart is most frequently present, and other concurrent cardiac malformations are not uncommon. The disease is one of infancy. As the diagnosis can be established with certainty only by autopsy, the mortality figures are unknown. In most cases reported in the literature the duration of the disease has been short. The most important clinical signs are cardiac enlargement, dyspnea, cyanosis, atypical murmurs, and dyspepsia. Three cases with typical histological changes are reported.

Fibroélastose endocarditique chez l'enfant.

La fibroélastose endocarditique était autrefois interprétée comme une endocardite foetale; mais, par la suite, on l'a décrite sous des noms bien différents. L'étiologie est imprécise, mais l'affection est considérée comme un trouble du développement. On trouve une augmentation du tissu fibroélastique de l'endocarde, d'ordinarie du côté gauche du cœur. Une importante cardiomégalie est souvent trouvée et l'existence d'autres malformations cardiaques concommitantes n'est pas rare. C'est une maladie du jeune enfant. Le diagnostic ne peut en être établi avec certitude que par l'autopsie; aussi, les chiffres de mortalité en sont inconnus. Dans la plupart des cas rapportés dans la littérature, la durée de l'affection a été brève. Les signes cliniques les plus marquants sont la cardiomégalie, la dyspnée, la cyanose, des souffles atypiques, et de la dyspepsie. Trois cas, avec des modifications histologiques caractéristiques sont ici rapportés.

Endocardiale Fibroelastose im Säuglingsalter.

Die endocardiale Fibroelastose wurde früher als fetale Endocarditis gedeutet, aber später wurde sie unter vielen verschiedenen Namen beschrieben. Die Ätiologie ist unbekannt, aber man glaubt, daß es sich bei dieser Krankheit um eine entwicklungsgeschichtliche Störung handelt. Man findet eine Zunahme des fibroelastischen Gewebes des Endocards, im allgemeinen in der linken Herzseite lokalisiert. Meistens ist eine bedeutende Herzvergrößerung vorhanden, und andere gleichzeitige Herzmißbildungen sind nicht selten. Es handelt sich um eine Krankheit des Säuglingsalters.

Die Mortalitätsziffern sind unbekannt, da die Diagnose mit Sicherheit nur bei der Autopsie gestellt werden kann. Bei den meisten in der Literatur berichteten Fällen ist die Krankheitsdauer kurz gewesen. Die wichtigsten klinischen Symptome sind Herzvergrößerung, Dyspnoe, Cyanose, atypische Geräusche und Dyspepsie. Es wird über drei Fälle mit typischen histologischen Veränderungen berichtet.

Fibroelastosis endocárdica en la infancia.

La fibroelastosis endocárdica fué primeramente interpretada como una endocarditis fetal, pero fué mas tarde descripta con diferentes nombres. La etiología es oscura, pero se cree ahora que la enfermedad es debida a un defecto del desarrollo. Hay un aumento del tejido fibroelástico del endocardio, generalmente localizado en el lado izquierdo del corazón. Hay un considerable aumento del corazón y puede haber otras malformaciones coexistiendo. Es una enfermendad de la infancia. Como el diagnóstico solo puede ser establecido por autopsia, la mortalidad es desconocida. En la mayor parte de los casos de la literatura la duración de la enfermedad ha sido corta. Los signos clínicos mas importantes son agrandamiento cardíaco, dispnea, cianosis, murmullos atípicos y dispepsia. Relato de tres casos con típicos cambios histológicos.

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SUMMARY OF SUPPLEMENT

Non-Bacterial Meningo-Encephalitides in children

by IVAR NILSBY

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Clinical experience suggests that meningo-encephalitis in childhood is more common than was formerly supposed, and it has been suggested that as the symptoms are often mild and non-characteristic, at least in children, many cases still remain concealed unless the possibility of mild meningo-encephalitis be continuously borne in mind.

It has also been stressed that even these mild forms of meningo-encephalitis are often followed by sequels, especially behaviour disorders, but hitherto no investigation, at least not on a large series, has been available in support of this belief.

With this in mind, all of the cases of meningo-encephalitis seen at the Pediatric Clinic, University Hospital, Lund, and classed as apparently spontaneous meningo-encephalitis, meningo-encephalitis after respiratory tract infections and CNS involvement in association with varicella were selected. These cases were studied in order to form a more detailed opinion of the clinical picture of these meningo-encephalitides (and as far as varicella is concerned, of the frequency of CNS involvement). The investigation included a review, at which the children were examined neurologically, psychically, psychometrically and in regard to their social adjustment. The observations made were compared with a control series.

Unlike earlier series on record, the present material included a large percentage of apparently mild cases of meningo-encephalitis and, above all, the results were judged in relation to a control series.

CNS-involvement in association with apparently mild infections of the respiratory tract was found to be fairly common, especially in children below 1 year.

The clinical picture of spontaneous meningo-encephalitis was not found to differ from that of post-catarrhal meningo-encephalitis: these groups did, however, differ with respect to age-distribution and seasonal occurrence. This suggests the possibility of difference in etiology, i.e. a viral origin for the spontaneous group and a toxic origin for the post-catarrhal group.

The early prognosis was as a rule good.

Of the 102 cases, 3 recurred during the time of the investigation. In all 3 the clinical picture was exactly the same as that described for the first attack. This suggests decreased local resistance following the first injury, a decrease that becomes apparent if the brain is exposed to some injurious factor, inflammatory or toxic.

Comparison of the patients in the spontaneous and post-catarrhal groups at the review showed no difference regarding neurologic, psychiatric or psychometric symptoms or social adjustment. These two groups were therefore taken together in the comparison with the controls. This comparison revealed a statistically significant difference between the patients and the controls regarding neurologic and emotional symptoms, mental development and most of the special tests used in the psychometric investigation. A statistical difference was also demonstrated regarding social adjustment. Many of the patients had difficulties at school, despite normal intelligence quotients. These school difficulties were due to a certain extent to emotional disturbances, mostly to special impairments; inability to integrate different perceptions, impaired memory and impaired attention. As the patients and the controls were comparable, with the exception that the patients had had known meningo-encephalitis, the difference between the observations made at the review must be regarded as sequels after meningo-encephalitis.

The frequency of brain injury in the patients, as compared with that in the controls, was taken as a measure of the frequency of sequels from meningo-encephalitides. As judged in this way, the frequency of sequels after these meningo-encephalitides was about 35 per cent.

All of the sequels showed a strong tendency to subside and to become less pronounced with increasing age. Those symptoms that persisted were as a rule mild and meant only a slight handicap for the patient, and only in a few isolated cases were the symptoms so severe as to lead to disability or social maladjustment.

The sexes were not found to differ regarding prognosis. Neither did the age at the time of the onset appear to be of prognostic importance. In the event of symptoms of meningitis only, or of meningo-encephalitides of rapid and mild course, the prognosis appears to be more favourable.

CNS involvement was found to be fairly common in varicella (22 per cent). It was observed as a mild clinical form of meningo-encephalitis or as asymptomatic pleocytosis. At review none of these children showed definite sequels attributable with certainty to the primary disease. In 1 child, however, severe, though transient, behaviour disorders were noted.

The cell and protein content of the CSF and the effect of previous puncture were studied in normal children.

On the basis of these studies the upper normal limit for the cell count for children above 3 months may be taken as 3 cells/mm^3. As for the protein content, Bisgaard 15 may be regarded as the upper normal limit.

For children below 3 months the upper limits for both the cell count and the protein content may be somewhat higher.

Earlier lumbar puncture has no effect on the protein content, but if the interval between two consecutive punctures is less than 8 days, the cell count may be increased.

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Proceedings of the Section for Pediatrics and School Hygiene of the Swedish Medical Society

Meeting, Falun, September 19, 1953

B. Hamne: **Communication on ileus conditions in the first year of life.**

The author pointed out the importance of personal collaboration with maternity departments in making earlier diagnoses of these conditions and thereby, in many cases, being able to prevent intestinal stenoses developing. Vomiting of yellowish material in the neonatal period does not always necessarily signify bowel origin, but one should in such cases make careful observation of the child with this possibility in mind. Direct roentgen examination of the abdomen studying the air distribution in the bowel is often sufficient for a diagnosis of duodenal obstruction. The discussion was illustrated by 5 cases of intramural atresia and stenosis respectively, and 3 cases of extramural obstruction of the duodenum. Obstructions below the duodenum are often multiple or otherwise complicated (in 1 case the small bowel ended blindly in a sac surrounded by massive adhesions and in another a large part of the small bowel was not canalised), and all the author's four cases died. Malrotation of the gut is associated, through the same retarded development, with a mesentery with a narrow attachment and this predisposes to volvulus of the whole intestinal canal. Contrast injection indicates the diagnosis but even without it operative indications are clear, but the operator must be prepared for surprises. Even if volvulus of the intestine has not occurred, symptoms of relative obstruction often exist because the caecum is fixed by adhesions over the duodenum. For early diagnosis and conservative treatment of intussusception (reduction with contrast injection), the author points out the necessity for recognizing the primary shock. The child becomes acutely ill, pale, cold and clammy and registers a low temperature. This condition passes over and is followed by intermittent colicky pains. Thus gradually an ileus condition develops and starts anew a condition of shock. The author's material (10 boys and 2 girls) with intussusception occurring before 1 year of age is evenly divided over the whole of the first year of life, from the age of 4 days to 11 months. Referring to 4 cases which the author, at any rate for the time being, would describe as pertinent, functional bowel stenoses were discussed. Clinically they show the ileus picture, and roentgenologically manifest stomach retention (in 1 case the contrast medium was retained for 29 hours) which greatly retards the bowel movements. The small bowel shows big variations and the contrast medium can be seen to be held up in the dilated portions before it is forced through the narrow ones. Clinically and roentgenologically, the condition is relieved so quickly that it cannot be a matter of stenosis due to organic disease. In one of the cases (premature) the escape of meconium was held up for 36 hours but in others it passed from the beginning, and therefore the author does not believe it was so-called meconium ileus but rather a transitory disturbances of innervation. Finally a case of persistent Meckel's diverticulum was shown where the

TABLE 1

Mortality in congenital obstructions

	Stockholm 1946—50	Paris (1953)	Boston (1953)		
			Number	Total mortality %	Present mortality %
Atresia of the oesophagus . .	20/31	14/17	233	53	33
Diaphragmatic hernia. . . .	2/9	5/6	91	16	11
Intestinal atresia s. stenosis .	3/14	8/10	211	55	33
Mesenter.commune	1/8	5/8	128	16	15
Meconium ileus.	3/4	1/1	63	67	21

bowel was kinked sharply against the base of the umbilical cord, so producing intestinal obstruction.

(To be published in greater detail in Sv. Läkartidningen).

Discussion: *Ehrenpreis:* As a starting point for a discussion on the results of treatment of congenital maldevelopments within the intestinal canal, demanding immediate surgical treatment, it would seem of interest to give an account of some recently published material from the special surgical departments of Children's Hospitals.

Stockholm's contribution is composed of a 5-year material from the Kronprinsessan Lovisas Children's Hospital, which was shown earlier at the meeting of the Nordic Paediatric Association in May 1951. In the material are included two types of congenital obstruction which are not listed in the table, because they are not correspondingly accounted for in the comparison material and moreover from the surgical viewpoint they hold this exceptional position that they can practically always be relieved with conservative treatment. These two groups consist of 5 cases of megacolon (among newborn) and 2 cases of meconium obstipation: these 7 cases, using conservative treatment, survived the neonatal period—the megacolon cases having been operated on successfully at a later date. With regard to cases of meconium obstipation some are reported in the literature, where the meconium which is not passed in the normal way shortly after birth, is retained in the rectum as a plug: these cases during the first days of life give the classical picture of a low ileus with increasing swelling of the abdomen, vomiting and total obstipation. This picture can neither be distinguished clinically nor roentgenologically from megacolon in the newborn. To improve the results in esophageal atresia as well as in the other groups, we must be decisive on three things: (1) earlier diagnosis, (2) increased centralization, and (3) improved pre-, para-, and postoperative treatment — *Gyllenswärd:* Hamne's address is a confirmation of the importance of the health supervision of the newborn by paediatricians—not merely consultation by calling the obstetrician. — *Kaijser:* Starting from Hamne's description of the so-called functional stenoses of the bowel. I would call attention to the difficulty of assessing correctly these conditions clinically. Two cases which I had the opportunity of following personally showed in the beginning a picture which in essential features resembled a definite bowel stenosis. On roentgen examination no complete obstruction to the contrast medium was revealed but one could demonstrate a considerably delayed emptying.

Greta Hedenström: **Case of erythroleukemia.**

(Published in this issue of Acta Pædiatrica).

Å. Björklund, N. Gellerstedt, B. Hamne, H. Sahlstedt and N. Tolagen: **A unique "lung case": Mediastinal cyst simulating bilateral pleurisy.**

A fifteen months old boy fell ill with a bronchial infection. He was admitted to the Children's Clinic of the Falun General Hospital where a diagnosis of bilateral pleurisy was made and bilateral thoracocentesis was performed. Roentgen investigation showed a bilateral exudate together with a paratracheal gland on the left side. Mantoux reaction was negative for 1 mg. Suction drainage was instituted but this did not lead to any result, for which reason, after some months, operation was performed and a large cystic tumor was extirpated: this tumor was situated in the anterior mediastinum and to the left but it extended also to the right. The tumor in its solid part could not be completely removed. PAD: Cystic teratoma of mature type (contained thymus and pancreas tissue). The patient was in good health six years after operation.

J. Söderberg: **Digitalis poisoning in a 2 year old boy.**

A hitherto healthy, two year old boy ate, in one lot, 33 tablets of Fol. Digital containing 0.05 g of Folium digitalis each: in all, 1.65 g. The patient was given a gastric lavage an hour after he had consumed the tablets but nothing resulted from it. About three hours later he became poorly, began to vomit and exhibited an irregular pulse. ECG the next day showed changes in the S-T segment with elevation in the first and second leads and depression in the third, and also first degree block with prolonged conduction time (0.24–0.26 sec.) and a temporary complete A-V block. The rhythm was uneven and somewhat slow—the pulse rate around 80 per minute. ECG on the third day after the poisoning, when the boy was otherwise normal, had ceased vomiting, felt well and when his clinical condition warranted no comment, showed periodical S-A block, temporary and complete A-V block besides the earlier S-T chances. The ECG changes returned to normal considerably more slowly than did the boy's general condition: conduction time was quite normal on the ninth day after the poisoning, but at the same time the depression in the S-T segment remained. Not until the next ECG, a month later, had the S-T changes wholly returned to normal. The boy displayed then a clinical condition free of any comment.

A. Berglund: **Concerning the relationship between Hand-Schüller-Christian syndrome and eosinophilic granuloma.**

Following a short historical account, and description of the clinical symptoms of Hand-Schüller-Christian syndrome, Letterer-Siwe disease and eosinophilic granuloma, it was pointed out that the histological picture of the foci can be very variable and alter from day to day. The clinical transition between the different disease entities, which has often been described (Letterer-Siwe disease which lasts longer than 6 months changes into Hand-Schüller-Christian-syndrome) was first shown by Wallgren in 1940. The transition between eosinophilic granuloma and Hand-Schüller-Christian syndrome has also been described. Such a case is demonstrated.

Discussion: *Karlén:* We have had in the Kronprinsessan Lovisas Children's Hospital during the last three years two cases, which showed that the lipoid strati-

fications in Hand-Schüller-Christian syndrome are secondary to some tissue injury. We have been able in the early stages of the disease to get pictures corresponding to Letterer-Siwe diseases. This is in favour of the opinion that they are only different forms of the same disease. Our first case was published in Acta Pædiatrica in May 1951. As for the second case I shall relate it briefly. It was interesting in that it showed a change from the picture of Letterer-Siwe disease to that of Hand-Schüller-Christian syndrome and this change occurred parallel with a large increase in blood cholesterol. This is the more remarkable considering the low age of our patient who died at one year and even then had manifested a completely typical picture of Hand-Schüller-Christian syndrome. — *Wallgren:* The more one's experience widens, the more convinced one becomes of the relationship between these different conditions. They constitute different states and not different diseases. For the diagnosis the roentgen examination is important and one ought to verify a negative finding after some time. I have seen a case of diabetes insipidus with a normal skull roentgen on the first examination, but which on control examination showed the typical "geographic map" appearance. Another case showed a normal sella at the first examination but a year later showed a distinct enlargement of the sella. — *Jelke:* Gave an account of a case of eosinophilic granuloma of the orbit in an adult.

Meeting, October 9, 1953

S. Ahnsjö: **Children's psychiatric department at Kronprinsessan Lovisas Children's Hospital.**

The present activity covers partly investigation, observation and treatment and partly outpatient advising, together with consultative work in the Hospital's medical and surgical departments. Since its inception on May 1st, the psychiatric department (12 beds) has dealt with 66 children and appears to have functioned very satisfactorily, and, not least, as a complement to its outpatient activities. This wide scope of its activities has been especially valuable in rendering possible a mutually stimulating co-operation between the Hospital's medical, surgical, röntgen, electroencephalographic and electrocardiographic departments.

C. G. Bergstrand and B. E. Hellström: **Double glucose tolerance tests in normal and fat children.**

The per oral double dose test has a relatively wide use as it is simple to carry out and according to some authors is more sensitive than the single glucose loading. Some figures from normal material among children have been published earlier. In this study 86 normal children in the age group 1–15 years have been investigated, consisting of convalescents in a children's hospital, in whom there has been no reason to suspect any disturbance in carbohydrate metabolism. In 23 normal cases the size of the dose has varied between 1 and 2 g respectively per kg body weight. Forty-six fat children have also been examined. The error in the method is 2% between two completely different testings. The normal cases show an increase, from an average fasting value of around 98 mg% to one around 140 after 30 minutes, with an upper limit of normal variation ($2\,^1/_2$ sigma) to 208. Corresponding figures after 60 minutes are also around 140 with an upper limit of 226. The Staub-Traugott effect is consequently restricted to stopping the increase which deviates from the relationships found

in adults. A division into a younger and an older age group demonstrates that in normal children there is a statistically certain higher fasting value for the older children (8–15 years) than for the younger ones (1–7 years). The difference is as high as 10 mg %. No difference is otherwise found in tolerance between the groups. If 2 g of glucose per kg body weight is given instead of 1 g after 30 minutes, the value is statistically higher but the difference is levelled out after 60 minutes. The carbohydrate metabolism of the fat children differs in no way from the normal curve.

Astrid Thilén: **Survey of penicillin and sulpha prophylaxis in rheumatic fever.**

A survey of the literature on sulpha and penicillin prophylaxis in rheumatic fever demonstrates all through a diminution of the frequency of sickness in the treated series, when compared with the untreated. What is of concern in the treatment of suspected streptococcal infections in all individuals, is to prevent the initial attack of rheumatic fever, and one adopts a somewhat expectant attitude when face to face with the widespread use of penicillin which in practice can bring this about. The risk that the way may be opened for penicillinase-forming organisms must be considered, despite the fact that, up to date, no reports concerning these have come to hand. Lung mycoses have been observed with intensive penicillin therapy. Cases of penicillin anaphylaxis are occurring with increasing frequency; therefore one warns against the use of penicillin in trivial infections. One queries whether the generally low immunity which ensues is, by itself, of any benefit. The prevention of streptococcal infections in individuals with early rheumatic fever should be of indisputable value, especially when considering the risk of recurrence.

Discussion: *P. Hedlund:* Those cases which we treated with sulpha were of course controlled without exception, as regards the blood picture and respiratory infections. The patient was instructed to take sulpha first when the risk of upper respiratory infection, especially sore throat, was thought to exist. Reports were given concerning the prophylactic treatment with sulpha in 10 cases of rheumatic fever, among young persons (St. Erik's Hospital). Sulphametinpyrimidin was given in one dose of 0.5 g morning and evening when someone in the family, class, or in near surroundings, fell ill with a condition which could be sore throat. Procaine penicillin, 50,000 units, have been given morning and evening. In the Epidemic Hospital in Stockholm, LUNDSTRÖM and I, in an attempt on a larger scale, have been able to show how relatively small doses of penicillin per os, given prophylactically to school children, lessened the number of streptococcal carriers to a great extent. Within a closed institution, Slagsta school and seminary, it was possible to combat a scarlatinal and sore throat epidemic among the children and personnel by giving all of them, about 300 altogether, a tablet of "Kabipenin" of 50,000 units, morning and evening for a week. Scarlatina and tonsillitis disappeared once the treatment began, and the number of carriers amongst the young children, which reached 80 %, dropped to 2 %. A disadvantage is the risk of increased resistance by other bacteria in the body, especially staphylococci. It must be remembered that this dreaded resistance increment does not carry the same risk now that we have a whole arsenal of effective antibiotics at our disposal, as it did some years ago.

C. G. Bergstrand, G. Birke, L. O. Plantin and R. Zetterström: **Steroid analysis in the adrenogenital syndrome.**

The excretion of the urinary steroids in the adrenogenital syndrome was studied in three boys (3–5 years old) with macrogenitosomia and in a newborn female pseudo-

hermaphrodite. One of the boys and the pseudohermaphrodite had definite signs of suprarenal cortical insufficiency. The excreted steroids were investigated by means of adsorption chromatography and infrared spectography. The result from the chromatography was compared with that obtained from investigations on adult men, and children of the same age as the three boys. From the chromatographic fractionization, no essential differences could be found between the three boys. The female pseudohermaphrodite showed on the contrary a completely abnormal chromatogram. During cortisone treatment (3 cases), the markedly increased difference in the total quantity of 17-ketosteroids lessened in all cases. At the same time normalization of the chromatogram became evident. In two of the boys some of the excreted ketosteroids were identified—some of these were pathological. Androsterone was excreted in large quantities and it is obvious that the marked virilizing effect is caused by this steroid. In the case of the pseudohermaphrodite no steroids could be identified.

Discussion: *B. Werner:* I had the opportunity of observing an interesting detail, in connection with the normalizing influence of cortisone on the 17-ketosteroid excretion, in cases of suprarenal cortical insufficiency in the newborn, some two years ago, when we had a very typical case in Sachsska Children's Hospital. The child was put on Doca and from 7 months of age on Cortisone too. The cortisone reduced the excretion of the 17-ketosteroids from 4 to 0.5 mg per twenty-four hours. The therapy was continued at short intervals for six months, following which the child, who had seemed apparently quite well, died suddenly. Notwithstanding the fact that the excretion of the steroids had all this time kept at a low level, post mortem examination demonstrated that no striking normalization of the suprarenals had occurred. Of course this cannot be excluded, since one does not know how they would have appeared without therapy, but together, they weighed 9.9 g (normal for a three year old child is 3 g) and had the typical formation corresponding to the condition.

Gunnar Ekström: **Septic coxitis or separated epiphysis in the newborn?**

An interesting case with regard to the differential diagnosis and especially the final diagnosis, occurred in the Kronprinsessan Lovisas Hospital recently. The girl was admitted when just under a month old for dyspepsia and was treated alternatingly by the internal pediatric and child surgical clinics. There was a very large hard swelling corresponding to the upper femur. She developed swelling of the back of the right hand corresponding to the second metacarpal, after some days. The girl was afebrile during the first $3\,^1/_2$ weeks and became febrile only in the last days of life. The white cell count varied between 13,200 and 24,800 but was usually around 15,000. The sedimentation rate rose sharply during the hospitalization, from 3 mm to 50 mm and stayed thereafter all the time between 50 and 60 mm. During the second week in the surgical department the diarrhoea and vomiting began again and during the third week she became more listless and difficult to feed. Cerebral complications were suspected. In the pediatric clinic the condition was thought to be osteomyelitis in the upper part of the femur. In the surgical clinic she was treated, in the first place, as a case of separated epiphysis of the upper part of the femur. At the same time, however, the patient received treatment as if she had a septic arthritis. She received heparin together with penicillin in big doses. Despite all these endeavors, the patient died after 31 days' treatment in hospital. At the post-mortem widespread osteoarthritis in the left hip joint with a large abscess was found. The partially fragmented head lay free in the abscess cavity; further there was an osteitis of the second right metacarpal: a large inflammatory focus on the front of the foramen magnum with marked

constriction of the spinal cord and compression of the medulla oblongata; the last-named focus was caused by osteomyelitis in the fore part of the foramen magnum, with extension to the soft parts and to some extent to abscess formation. The röntgen resemblance in this case with those described earlier in the literature as separation of the epiphysis of the upper part of the femur, due to birth trauma, was striking. The resemblance was confirmed by a demonstration of röntgen pictures and lantern slides. The typical röntgen finding in cases of separated epiphysis in the upper femur, is an increased distance between the acetabulum and the ossified part of the femur, that is to say, lateral displacement of the femoral shaft, quickly forming callus, sometimes club-like in appearance, around the upper part of the diaphysis and sometimes subperiosteal callus low down in the diaphysis, which often descends to the middle of the shaft and many times even down to the lower femoral epiphysis.

Discussion: *C. Gyllenswärd:* The child was admitted late and in bad condition: was almost moribund. The absence of fever in a young child does not speak against a septic infection, since such a bad case may have a lowered temperature. For a correct diagnosis a puncture would naturally have been of value, but since no fluctuation whatever could be demonstrated, this was omitted. — *Ekström:* Separation of an epiphysis due to birth trauma occurs mostly in the lower part of the femur, in the upper and lower parts of the humerus, in the upper tibia and also sometimes in the upper part of the femur, but this last type is unusual. The condition occurs usually in breech deliveries and particularly so in first-borns. The typical clinical symptom is swelling of the traumatized extremity. The oedema is often very firm. Only obvious shortening of the extremity in question can be observed easily. The child holds the injured extremity still (pseudoparesis) and shows distress on passive movement. Often the skin is discolored a bluish red and at times crepitus can be elicited. After a couple of weeks, a massive bone-like thickening of the injured extremity can be recognized. The cortical bone in the injured epiphysis often ossifies much earlier than normally. The prognosis is usually surprisingly good but epiphyseal separation with obvious displacement ought to be treated according to surgical principles with reposition and fixation.

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BOOK REVIEWS

S. Z. Levine: **Advances in Pediatrics, Vol. VI.**

The Year Book Publishers, New York, 1953. 323 pp. Sw. cr. 42.

The sixth volume of "Advances in Pediatrics" contains several reviews of different sections of pediatrics. The monographs, written by specialists dealing directly with their particular subjects, treat the actual problems which arise, especially those problems dealing with developments during the last few years. Here, few pediatricians, except those specially interested in the particular subjects, have been able to follow the rapid advances which have occurred. The reviews are very good and report in an excellent manner the results which have been achieved.

In the first mongraph, "Lymphosarcoma in childhood" written by Harold W. Dargeon, a report is given of symptomatology and treatment, based on the author's own experience of 50 cases. The signs and symptoms of this disease are usually very distinct from those of leukemia; it may happen, however, that a case, initially a typical lymphosarcoma, develops later into a leukemia. An intensive treatment is recommended because the prognosis does not seem to be absolutely hopeless. Theodore H. Ingalls has, in a chapter entitled "Preventive prenatal pediatrics", discussed various factors that may influence the production of congenital malformations. Strong support is given to beliefs that other previously not accepted causes may exist and should be taken into consideration in the development of congenital malformations. In "Intestinal obstruction in the neonatal period" C. Everett Koop gives an excellent review of the symptomatology and treatment of these disorders. The necessary intimate cooperation between pediatrician, roentgenologist and surgeon is stressed, as is also the importance of early operative treatment. It is maintained that it is better to perform an exploratory laparotomy, even if localisation of the obstruction has not been definitely settled, rather than to make further examinations which may fatally postpone a life-saving operation. "Hemolytic disease of the newborn" by Philip Levine, contains above all a review of our present knowledge concerning the serological aspects of this disease; in this respect the article is very exhaustive. In a special chapter a report is given of the cases which are produced by an incompatibility within the A-B-O system; in another chapter problems regarding the etiology and the prevention of nuclear jaundice are discussed. Edith L. Potter's chapter on "Pulmonary pathology in the newborn" is very profitable reading. The review, based principally upon the author's own researches and practical experience, gives a clear physiological background to the development of the pathological disorders. Those who are interested in the physiology and pathology of the newborn period will get new ideas for continued research work. A review of "The lipoidoses" has been written by S. van Creveld. The different disorders that have been referred to under this generic term, have been treated, each one separately. The old division of diseases has been maintained. The author stresses the difficulty of deciding whether these diseases are produced by a disturbance in the lipoid metabolism, or whether the lipoid storage is a purely

secondary effect of some other primary process. The similarity and the connection between Niemann-Pick's and Tay-Sachs' disease on the one hand and different types of reticuloendothelioses on the other hand is stressed. The last chapter, written by Wolf W. Zuelzer, on "Megaloblastic anemia of infancy", contains a report of his own wide experience in this field and gives the records of some twenty new cases of this disease.

All these monographs are of great scientific value and give much impulse for continued research work.

Rolf Zetterström, Stockholm.

Prematurity, Congenital Malformation and Birth Injury.

Proceedings of a Conference Sponsored by the Association for the Aid of Crippled Children at the New York Academy of Medicine, New York 1953. 255 pages. Price $ 4. (Can be ordered from the Association for the Aid of Crippled Children, 345 East 46th Street, New York 17.)

In this book about 30 of the most prominent scientists from various parts of the United States have discussed problems relating to new-born and premature infants. The contents are extremely interesting and the book should be read by everyone who has to deal with new-borns. It is an adequate present-day outline of our knowledge in this important field of pediatrics.

G. Romeo, R. Gavini and *V. Mattina:* **Morbo di Cooley e Alterazioni Metaboliche.**

Collezione di Monografie Pediatriche. Editricae Catania, 1953. Price Lire 1,500.

This volume contains the report of a study on 8 children suffering from Cooley's disease. A normal trypsin content was found, a more or less marked steatorrhoea with deficient fat absorption, abnormal glucose tolerance curves, normal blood calcium and moderate hypophosphatemia. The authors believe that the cause of the metabolic disturbances is some disorder of adreno-cortical function.

Goodrich C. Schauffler: **Pediatric Gynecology.**

The Year Book Publishers, Inc., Chicago, 1953. 3d Edition. Price $ 7.50.

The third edition of this well-known book has been thoroughly revised and new chapters added. Gordon Robertson has written a chapter on embryonic development of the female genital system; a chapter on urology is contributed by Elmer Belt and Clarence V. Hodges, and a chapter on proctology by Donald R. Laird. The 300 pages give very valuable information on the treated subjects and the volume should be available in every pediatric library.

S. Garcia-Vicente: **Aportación de la escuela española a la técnica endobronquial.**

Análisis cronológico y doctrinal. Conferencia pronunciada en la Real Academia Nacional de Medicina, Madrid, 1953. 43 pages.

The author discusses the contribution of Garcia-Vicente's works to the development of modern endobronchial techniques.

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NEWS AND COMMENTS

Centre International de l'Enfance

Le Centre International de l'Enfance, Paris, organise en 1954 cinq cours qui sont les suivants:

I—*Cours sur l'Adaptation de l'enfant atteint d'infirmité motrice*, du 11 Janvier au 21 Février 1954; 30 participants.

Ce cours est destiné à l'ensemble du personnel appliqué à l'adaptation fonctionnelle, professionnelle et sociale des enfants atteints d'infirmité motrice: médecins, physiothérapeutes, assistantes sociales, éducateurs, psychologues, travaillant en équipe.

L'enseignement comprend à la fois les problèmes fondamentaux de physiologie et de thérapeutique nécessaires à la compréhension générale de l'infirmité et de la réadaptation fonctionnelle, et les questions de psychologie, de pédagogie, de pré-orientation professionnelle, de pré-apprentissage, de réintégration de l'infirme dans la famille et la société. Il comporte, à côté d'exposés suivis de discussions et de cercles d'études, des stages et visites dans les services hospitaliers et sociaux, ainsi que dans des institutions de réadaptation, d'éducation, d'orientation professionnelle et d'adaptation au travail.

II—*Cours et seminaires sur les Facteurs prenataux du developpement de l'enfant: Progenèse: applications médicales et sociales*, du 8 Mars au 5 Avril; 25 à 30 participants.

Envisageant l'ensemble de facteurs héréditaires et non héréditaires qui préexistent à la fécondation et qui concourent à la formation de l'être et à son développement, ce cours est conçu principalement en vue des applications pratiques qu'on peut en tirer dès maintenant, et qui permettent aux médecins de conseiller utilement les familles pour éviter, dans la mesure du possible, l'apparition des maladies hérèditaires.

Il est destiné à des médecins de disciplines assez diverses, pédiatres, médecins responsables des services d'hygiène et de prophylaxie, administrateurs, démographes, etc.... tous possédant déjà de sérieuses notions de pathologie héréditaire, d'où la possibilité d'organiser partiellement ce cours sous la forme de séminaries et de discussions.

III—*Cours de Pédiatrie sociale*, du 26 Avril au 18 Juillet.

Le programme comporte toutes les grandes questions concernant l'action médico-sociale et sociale en faveur de l'enfance, normale ou non. Il a un caractère pratique marqué par un grand nombre de visites, de stages dans des centres médico-sociaux et des établissements pour enfants et surtout par de nombreuses discussions et cercles d'études. Ces derniers sont pour la plupart dirigés par les participants eux-mêmes avec apport de documents provenant de leur propre pays en vue d'une large information internationale. Le travail en équipe des spécialistes de l'enfance est particulièrement envisagé.

Le cours réunira environ 30 médecins, de nations différentes, soit pédiatres, soit fonctionnaires sanitaires responsables de la protection maternelle et infantile.

IV—*Cours sur la Prévention et le traitement de la tuberculose de l'enfant*, du 11 Octobre au 7 Novembre; 30 participants.

Ce cours s'adresse à des médecins, soit pédiatres, soit administrateurs sanitaires responsables des programmes de lutte contre la tuberculose ou chargés de l'organisation de la vaccination antituberculeuse, en liaison avec les programmes de l'UNICEF et du WHO.

Profitant de l'expérience acquise dans de nombreux pays, sous des climats très différents, par les équipes internationales de vaccination, par le BCG, et de celle de chercheurs de tous les pays, l'enseignement se présentera essentiellement sous forme de démonstrations et travaux pratiques, discussions dirigées et cercles d'études.

V—*Cours pour la Formation de travailleurs sociaux pour enfants*, du 8 Novembre au 19 Décembre.

Ce cours groupera 25 à 30 participants choisis parmi le personnel supérieur des travailleurs sociaux de différents pays. Il reprend dans ses grandes lignes le programme de pédiatrie sociale pour médecins, mais il est adapté à un auditoire ne comprenant que des travailleurs sociaux. Il étudie l'aide sociale que l'enfant doit obtenir aux différentes étapes de son développement, depuis la période prénatale jusqu'à son adolescence — qu'il s'agisse de l'enfant normal ou de l'enfant physiquement diminué, infirme, inadapté ou en danger moral. Il est compris surtout comme un enseignement pratique avec de nombreuses visites, stages, discussions, de façon à montrer la nécessité d'une coordination dans les efforts entre les travailleurs sociaux, les médecins, les organismes de sécurité sociale, les administrations, les services spécialisés, les œuvres privées et les organismes internationaux.

The 11th Nordic Pediatric Congress

The 11th Nordic Pediatric Congress will be held in Oslo, Norway, from June 29th to July 1st, 1954. The Congress will be inaugurated on June 29th at the Auditorium of the University, followed by a plenary session on Cerebral Paresis with introductory reports by P. Plum and L. Salomonsen. Two other plenary sessions (June 29th and July 1st) will take place at the Norwegian Medical Society, one dealing with the Electrolyte Balance in Dehydration in Infants, the other with Neonatal Asphyxia. On June 30th a round table discussion on the Possibilities of Physical Diagnosis in Congenital Malformation of the Heart is planned. On the same day the reading of papers on free subjects is scheduled. President of the Congress is Professor Leif Salomonsen and General Secretary Dr. Arne Njå.